OVERSIGHT

HUMAN TOTAL BODY IRRADIATION (TBI) PROGRAM AT OAK RIDGE

HEARING

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT

OF THE

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SCIENCE AND TECHNOLOGY
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OVERSIGHT—HUMAN TOTAL BODY IRRADIATION [TBI] PROGRAM AT OAK RIDGE

WEDNESDAY, SEPTEMBER 23, 1981

House of Representatives,
Committee on Science and Technology,
Subcommittee on Investigations and Oversight,
Washington, D.C.

The subcommittee met, pursuant to call, at 9 a.m., in room 2318, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Mr. Gore. The subcommittee will come to order.

In 1957, under the sponsorship of the Atomic Energy Commission, the Medical Division of the Oak Ridge Associated Universities began a program of treatment for cancer patients designed to improve various radiation therapies as well as to assess the health effects of total body irradiation.

Later, beginning in 1964, the National Aeronautics and Space Administration began to provide additional funds for these experiments to include the objective of measuring the biological effects of low radiation doses and low dose rate exposures. NASA hoped to use this information to predict the onset of acute radiation sickness in astronauts. From 1957 to 1974, nearly 200 patients received treatment at the Oak Ridge facilities, including a boy named Dwayne Sexton.

In August of this year, a national magazine published an article entitled "How the Space Program Experimented with Dwayne Sexton's Life." This article alleged that the Oak Ridge facilities were substandard, that the treatments were of little therapeutic value and inferior to other techniques that were available, that fully informed consent was not given and, most importantly, that the attempt to gain data for the space program took precedence of the treatment of patients.

When I first became aware of the allegations against the Oak Ridge Medical Division early in this year, it seemed to me important to look carefully at all the facts surrounding the development and execution of this program.

In dealing with incidents that occurred decades ago, I wanted to be sure that we gained as accurate a view as possible of the treatments that were available for cancer patients in the United States during this program, the ethical standards to which physicians could legitimately be held, the kinds of controls that were exerted from the sponsoring agencies on this program, and the nature of the decision processes at the Oak Ridge Medical Division. In order to accomplish these purposes, as well as to investigate the specific allegations, I authorized the subcommittee to begin an independent investigation of the program that culminates in today's hearing.

The allegations that have been made are serious ones. They go to the core of what medical practice is supposed to be about in this country and raise again profound questions about our ability to conduct ethical human experimentation.

Perhaps the most important question is whether the people involved in this program were treated in the best possible way for their welfare or whether they were in any way dehumanized in the search for some other social good. Not only is this important to know for the good of the families and the people who were treated at Oak Ridge, but it is also important to know for a society that is struggling with the ethical consequences of rapidly advancing technology.

Today we will want to give the agencies and the people involved in this program the opportunity to present evidence and express their thoughts and their feelings about what happened at Oak Ridge. The subcommittee will be asking hard questions to make sure that all the facts of the matter are fully known. It is only through an explication of the facts that we will begin to know what really happened.

I would like to call on the ranking minority member, Mr. Walker.

Mr. WALKER. Thank you, Mr. Chairman.

One of the most difficult duties that an investigatory subcommittee has is to have to go back and attempt to critically examine a federally funded program many years after the fact.

The passage of time dims memories, facts tend to become clouded, critical witnesses die or move away, and recollections tend to become selective. All of these factors tend to make the job of factfinding almost impossible.

Very serious allegations have been made against Oak Ridge Associated Universities Medical Division and against NASA and what was originally the Atomic Energy Commission and is now the Department of Energy.

We are not doctors, but we hope that our witnesses today will give us enough information so that we will be able to form a fair judgment on this program based on the context of the times in which it was in operation.

It is axiomatic that inherent in all human progress is an element of risk. Others have charged that the participants in this program forgot their hippocratic oaths and treated their patients with a reckless disregard for their health and welfare. That the radiation treatment used at Oak Ridge embodied great risk is beyond question. But those who were treated at Oak Ridge were already in great danger.

Only those who have escaped the deadly grasp of cancer, or those who have shared with a loved one the absolute despair of facing certain death can understand that no risk is too great, no probability of success too small. Just as we will examine the evidence and attempt to determine if the program was medically sound in the context of the times, we must also examine the medical ethics involved.

Victims of cancer are not always able to best determine what treatment is best for them. The decisions require a great deal of help from the doctors involved. Treatments must be fully explained. Risks must be spelled out in detail. The process is known as informed consent. The patient must be given full disclosure of all the facts so that his decision may be made with full knowledge of all potential consequences.

There is a fine line which separates treatment of a patient which results in the advancement of knowledge and experimentation designed to advance knowledge which happens to benefit the patient. We will attempt to determine if that line became blurred at Oak Ridge.

Finally, our hearing today is important because we are dealing in an area in which serious allegations have been made. Professional reputations have been tarnished. It is only right that all sides have the opportunity to present evidence to support or refute those allegations and to face questions from an impartial panel. If those allegations prove correct, we will support remedial actions to insure that they cannot occur again. If they are unfounded, the facts will clear the stigma from the researchers involved.

Thank you, Mr. Chairman.

Mr. GORE. Thank you very much.

We have a lengthy witness list today and we are going to move right into the hearing, and I would like to call our first witness to come forward, Mrs. Mary Sue Sexton.

We are pleased to have you with us, Mrs. Sexton. If you would come up to the witness table, to that center chair there.

We have a practice, Mrs. Sexton, as an investigative subcommittee, of swearing in all our witnesses. You have no objection to being sworn, do you?

Mrs. SEXTON. No; of course not.

Mr. GORE. Would you raise your right hand? Do you swear the testimony you are about to give will be the truth, the whole truth and nothing but the truth, so help you God?

Mrs. SEXTON. I do.

Mr. GORE. Thank you and welcome. Now you are accompanied by a friend?

Mrs. SEXTON. Yes.

Ms. TUCKER. Kitty Tucker. I am an attorney.

Mr. GORE. Kitty Tucker, you are representing her as counsel?

Ms. TUCKER. Yes, and as a friend.

Mr. GORE. Fine. That is fine. If you are going to be giving testimony we will swear you, but if you are simply going to advise her——

Ms. TUCKER. I will simply advise her.

Mr. GORE. Fine. Mrs. Sexton, we are pleased to have you with us today and you may proceed with your statement. Without objection the entire text of it will be put into the record and if you want to present it orally or if you want to read it, either way is fine, you go right ahead.

TESTIMONY OF MARY SUE SEXTON, KINGSPORT, TENN., ACCOMPANIED BY KITTY TUCKER, ATTORNEY FOR MRS. SEXTON

Mrs. SEXTON. Thank you.

My name is Mary Sue Sexton and I'm from Kingsport, Tenn.

My son, Talmon Dwayne Sexton, died at the Oak Ridge Institute of Nuclear Studies in Oak Ridge, Tenn., on December 29, 1968. I'll carry the memories of that day and many more days we spent at the clinic for the rest of my life.

In the past few months I have learned more about what happened to Dwayne and me than I was told the entire time we were there. What I have learned has made me sad and made me hurt and also angry, and has made me come here today. I have come to tell you how we were betrayed, how we were lied to and misled. I have come to tell you because little Dwayne cannot.

My husband Talmon and I took Dwayne to Oak Ridge after our family doctor told us Dwayne had aplastic anemia. He took sick in July 1965. After the doctors at Oak Ridge examined Dwayne, they told us he had acute lymphatic leukemia. The doctors told us they wanted to try a new treatment on Dwayne. They said it was promising enough that it could help Dwayne and might even prove to be a cure for the leukemia. We were told they would use standard treatments if we so chose, but they said the standard treatment would only offer a short life for Dwayne at best. We agreed to try the experiment.

Blood tests were run on Talmon and me and I was found to be compatibly matched with Dwayne's blood type, which was O positive. Talmon's blood type is B positive. We decided it would be worth the risk to try the experiment because the doctors convinced us it was really Dwayne's best chance.

The experiment involved taking some of Dwayne's bone marrow out, giving it radiation, and then injecting it into me. A few days later, the doctors made an incision in my thoracic duct, just above my left collarbone, and a fluid was drained from me, filtered, and then injected into Dwayne. The doctors hoped that my body would build up antibodies which would fight off Dwayne's leukemia. Before the bone marrow transfer, Dwayne was put into a remission with chemotherapy.

Just a month ago I received a copy of a report the doctors wrote about Dwayne's treatment. It's titled "Treatment of Acute Leukemia: An Experimental Immunologic Approach," and written by C. L. Edwards, C. C. Congdon, N. Genbozian, H. Vodopick and G. A. Andrews. In that report the doctors said there was a possible hazard to me involving the transmission of the leukemia. The doctors never told me of that possible hazard. In fact, they told me that leukemia or cancer had never been given from one person to another. Even if I had been told of the danger, I would have gone ahead anyway with the experiment because I thought it might have saved Dwayne's life.

The doctors' report also said there were risks to Dwayne involved with the experiment, including, and I'm quoting now, "deprivation of conventional chemotherapy." The report says that, and I'm quoting again, "maintenance therapy was withheld for 16 weeks to permit further observations after the experimental treatment."

When I read that report, it was the first time I learned that by depriving Dwayne of chemotherapy his life might be endangered. In fact I was never told there was such a thing as maintenance therapy. I thought the medication was stopped because it wasn't needed any more.

In the 13 years since Dwayne died I've learned a lot about cancer and leukemia. I've learned that early detection is important and I've learned that maintenance therapy is critical. I now believe that Dwayne might have been kept in remission if the doctors had treated him properly with chemotherapy at the beginning. He might be alive today. They made my baby a guinea pig.

I have since learned that the type of treatment they tried on Dwayne had never been tried on a human being before, only rats. I was never told that Dwayne was the first human used for this experiment.

At the time of the bone marrow transfer I was 24 years old. I was sick with worry after I had just been told my 3-year-old child had leukemia. I believed everything the doctors told me. I asked many questions and I was told things that I have since learned were just not true. Both Talmon and I signed a consent form when we agreed to the experiment. The form said that the alternatives and the hazards were explained to us. They were not fully.

After 4 months without therapy, Dwayne relapsed. I insisted that the doctors begin treating Dwayne with the standard treatment, which was chemotherapy. The doctors thought it was worthwhile to try the bone marrow transfer again on Dwayne and his dad, even though they were not compatibly matched. I refused because I did not want anyone else to take the risk of being injected with leukemia cells. Dwayne was started on chemotherapy again.

For about 3 years Dwayne was in remission, though he relapsed five to seven times. In November 1968 he began hemorrhaging and we took him back to Oak Ridge. The doctors told us Dwayne had relapsed again. I wrote in my journal what they told me. There were three treatments available, the doctors said. One was blood transfusions. One was more chemotherapy, and the other treatment was radiation. The doctors told us that Dwayne's best chance was with radiation, so we told them to use whatever was best for Dwayne. They chose radiation.

Dwayne was exposed in METBI for 3½ hours. I stood outside the room the entire time and watched. After that he was taken to LETBI and hooked up to a monitoring belt. The doctors were watching him closely. In just the past week I've received a copy of Dwayne's medical records. They show that the day he received his radiation treatment Dwayne already had an infection that was discoverd in a nose swab. The doctor's records of that day's treatment says, and I'm quoting again:

> The patient received 353 R exposure which gave an average total body dose of 265 rads. The patient experienced no adverse effects during the time of irradiation and amazingly did not have any vomiting or nausea during the time of exposure or immediately thereafter.

The only way I learned that the equipment used to monitor Dwayne was provided by NASA was when one of the technicians, Annie Sipe, mentioned it to me in passing. Today I believe that they hooked Dwayne up to that belt just so they could watch him to see if the radiation made him sick. It was because they wanted to find out at what point radiation would cause vomiting when the astronauts were in space. Later, when Dwayne was critically ill, they never hooked him up.

I want you to know that I did understand some treatments at Oak Ridge were experimental. But we were told they would do the very best for the patient's benefit first of all. We were told the experimental bone marrow transfer could possibly be a cure for Dwayne. Also, we were told there was a possibility the radiation therapy could bring about a permanent remission if Dwayne were kept away from infections. But in fact, Dwayne already had a serious staph and pneumonia infection reported to the doctors before Dwayne took the 353 roentgens of radiation in one session of 3 hours and 38 minutes.

The reason we kept Dwayne at Oak Ridge was because we were told they had the very best treatment that was available anywhere. Since then I've learned that doctors at St. Jude's Hospital in Memphis were treating children with leukemia using chemotherapy as early as 1962. And by 1965 they had cured 17 percent of them. How many children were cured with radiation at Oak Ridge? How many children were cured with these bone marrow transfers at Oak Ridge? Dwayne was not.

It's been said by the Oak Ridge doctors that they gave their patients excellent care. We loved those doctors, technicians, nurses, and the other patients that were there. I didn't mind the pain I went through when the doctors cut open my thoracic duct. Dwayne didn't mind the pain of the bone marrow tests, even though he suffered so. I didn't mind when they injected leukemia cells into me. I didn't mind any of it. I was grateful for a chance to keep my baby from dying. But now I know that Dwayne was just a guinea pig for an experiment that had never before been tried on human beings. Now I know that I was a guinea pig too. And now I do mind.

Since Dwayne's story was published in Mother Jones magazine, the newspapers back home in Tennessee have been full of articles about people who say their lives were saved at Oak Ridge. I'm happy for them, but I'm sad for Dwayne. I'm sad for Ramona, Jimmy, Roy, Dennis, Bobby, Jerry, Jennifer, and all the other little children who died at Oak Ridge. I know that death is a part of life and Dwayne knew it too. He wasn't afraid to die. I was prepared for his death, but I wish he was here today to tell you how he was used.

I trusted the most precious thing I had on this Earth to the doctors at Oak Ridge, the life of my baby son. My trust, and Dwayne's trust, was betrayed.

Thank you for the opportunity to tell what Dwayne cannot.

Mr. GORE. Thank you, Mrs. Sexton. I know that is awfully hard for you. We can take a short recess if you want before we go to questions, if that would be easy for you.

Mrs. SEXTON. That is fine.

Ms. TUCKER. She is ready now.

Mr. GORE. OK.

In the course of our investigation into this, we may ask for information or testimony later on regarding the medical treatment provided to Dwayne and to you and it may be necessary for you to give your permission for us to get such information and testimony relating to the medical records.

I take it you have no objection to that.

Mrs. SEXTON. I have none at all.

Mr. GORE. Where did you first go to have your son's illness diagnosed or checked?

Mrs. SEXTON. I went to Dr. Leeds in Oneida, Tenn. Then they placed him in the hospital for 4 days in the Scott County Hospital, where they ran many blood tests. I asked him pointblank on the third day, I said, "Does Dwayne have leukemia, because of all these blood tests?

He said, "No, Mrs. Sexton, he does not." He told my husband after Dwayne was released on the fourth day that he thought Dwayne had aplastic anemia. He made arrangements for us to take him to Oak Ridge to see what was causing the aplastic anemia which I thought was the matter with him.

Mr. GORE. So the first doctor you consulted was the one who referred you to Oak Ridge?

Mrs. SEXTON. Yes, sir, he was.

Mr. GORE. What were you told when you got to the Medical Division at Oak Ridge?

Mrs. SEXTON. After he was examined, we were told he had acute lymphatic leukemia.

Mr. GORE. And they told you that you had a choice of the more conventional treatments?

Mrs. SEXTON. Yes. Of course I knew nothing of what the treatments were for leukemia, but they said they thought the best for Dwayne possibly could be this new experiment they would like to try for him, for his benefit.

Mr. GORE. Now you referred in your statement to the fact that you had learned later, that another hospital, St. Jude's Hospital at Memphis——

Mrs. SEXTON. Yes, sir.

Mr. GORE [continuing]. The traditional, or conventional rather, chemotherapy was getting 17 percent cure rate?

Mrs. SEXTON. Yes, sir.

Mr. GORE. We will ask about that figure later on, but at the time the people at Oak Ridge said they felt that the percentage of cure with conventional treatment was 3 or 4 percent. Now leaving aside whether they were wrong about that or not, do you remember that figure being given to you at all?

Mrs. SEXTON. No, sir. Possibly if it was I do not remember it, but even 1 percent is better than nothing.

Mr. GORE. Now did they describe the experimental procedure in some detail to you, did they tell you what it involved?

Mrs. SEXTON. They told me what they were going to do. I said if we did go into this, they told us they were hoping the antibodies built by my body would help Dwayne's system fight the leukemia. Chemotherapy was withheld from Dwayne from the start of the infusion of the antibody serum. When treatment was stopped I saw nothing wrong, I thought the experiment was working for him. I thought it was doing it's job.

Mr. GORE. I want to ask you some questions about that procedure, but in order to fit it into the context of this hearing I would say for those trying to follow this that there are two separate focuses in the hearing, the larger questions involving the dual goals of the experimental program at Oak Ridge, the treatment of patients and the acquisition of knowledge and how those goals interacted; then a narrower focus on the specific case involving your son.

Mrs. SEXTON. Sure.

Mr. GORE. Now as we look at the specific case involving Dwayne, there are separate issues there. The radiation treatment didn't really come until much later, right?

Mrs. Sexton. Right.

Mr. GORE. The first issue that you have raised in your statement is the selection of this experimental immunotherapy technique that you went through with your son. But let me get the times right in my own mind.

Dwayne was first taken there in 1965?

Mrs. SEXTON. Correct.

Mr. GORE. What month?

Mrs. SEXTON. On July 27.

Mr. GORE. July 1965. And his death was in December 1968?

Mrs. SEXTON. That is correct.

Mr. GORE. Three and a half years later.

The first treatment given was this experimental immunotherapy?

Mrs. SEXTON. They gave him 2 weeks' treatment of methotrexate 2.5 grams or milligrams I believe it is—I have it in the documents—and 40 milligrams I believe it is, the prednisone for 2 weeks. After the 2 weeks, methotrexate was withheld from day 1 of the cellular infusion and on the third day the prednisone was discontinued too. This went on for 16 weeks without any treatments at all.

That is my question, why withhold it for 16 weeks?

Mr. GORE. We are going to ask that question to the doctors and the specialists, but I want to get clear in my own mind exactly what the course of events was.

First of all, they embarked on this immunotherapy and the first step was to give your son chemotherapy?

Mrs. SEXTON. Sure.

Mr. GORE. Which is part of the standard treatment for leukemia. They took some of the cancerous cells from your son, they gave him chemotherapy and they got——

Mrs. SEXTON. They got cells, first of all.

Mr. GORE. That was first?

Mrs. SEXTON. Yes, sir, it was.

Mr. GORE. All right.

Then they took some of the cancerous cells out of your son and irradiated them to kill the leukemic quality of the cells?

Mrs. SEXTON. That is what they were trying to do.

Mr. GORE. And then they put those cells, after they had been irradiated, into you?

Mrs. SEXTON. Four syringes they injected in my arms and my hips.

Mr. **Gore**. Your arms and your hips. Then they waited for your body to develop antibodies to fight the leukemic cells?

Mrs. **Sexton**. That is right.

Mr. **Gore**. For several weeks, 16 weeks?

Mrs. **Sexton**. No; they waited on that for 2 weeks.

Mr. **Gore**. Two weeks?

Mrs. **Sexton**. Right.

Mr. **Gore**. And then they——

Mrs. **Sexton**. In the meantime, in 2 weeks he was on chemotherapy while they were waiting for my antibodies to build up.

Mr. **Gore**. All right. While you were building up antibodies, Dwayne was continued on chemotherapy?

Mrs. **Sexton**. Two weeks, yes.

Mr. **Gore**. For 2 weeks. Then they conducted a surgical procedure on you to remove whatever substance they felt would contain the antibodies that you had developed and inserted them into Dwayne?

Mrs. **Sexton**. Intravenously.

Mr. **Gore**. Intravenously.

At that point they stopped the chemotherapy that Dwayne had been receiving. That is the first question that you have, why that chemotherapy was stopped at that point? We will ask that question.

Mrs. **Sexton**. And even, after so long, I noticed in November that it looked to me like Dwayne had already started getting peaked, he was going downhill. He was going back for his blood tests. Why wait 16 weeks, instead of back in November; 4 more weeks, start it up again, why wait?

Mr. **Gore**. Why wait then?

Mrs. **Sexton**. Yes.

Mr. **Gore**. All right. Now this is a question we will ask. But I want to make it clear that this is really separate from the whole question involving NASA and the goal of acquiring data for the space program or on radiosensitivity generally. But it is an important issue and I take it you believe that it is reflective of your concern that experimental procedures were given precedence over treatment.

Now we will inquire into that issue. But now next, after this procedure was conducted, your son experienced a relapse, is that right?

Mrs. **Sexton**. Yes.

Mr. **Gore**. About how long after that?

Mrs. **Sexton**. From the start of the infusion, it was 16 weeks, they said he was in relapse again.

Mr. **Gore**. At that point they went back to chemotherapy, right?

Mrs. **Sexton**. They went to vincristine with chemotherapy.

Mr. **Gore**. OK. Your son then lived another 3 years. During this time he was continued on chemotherapy?

Mrs. **Sexton**. Yes, on alternating types of chemotherapy.

Mr. **Gore**. Had they ever given you an estimate of how long your son would live when the leukemia was first diagnosed?

Mrs. **Sexton**. They did not.

Mr. **Gore**. We will inquire into that matter also, but it is my understanding that at that time the predictable lifespan was really quite short. I do not know the exact figure, but we will ask about that.

All right. At the end of this 3 years' worth of chemotherapy, your son finally had a more serious relapse than the others? I believe there were four relapses altogether.

Mrs. SEXTON. No, sir, there was five, six, I know doctors documented at least five in medical records, maybe six.

Mr. GORE. The final one was more serious than the other ones?

Mrs. SEXTON. They seemed to think so.

Mr. GORE. They seemed to think so but such signs were not visible to you?

Mrs. SEXTON. I only noticed his nose was bleeding; he looked perfectly healthy to me looking at him, but blood tests and bone marrow, they tell the real story.

Mr. GORE. Yes. At that point they told you that the chemotherapy approach wouldn't work any more?

What they told me is that they had tried all the conventional chemotherapies and there weren't any more to try. They could move to a new combination chemotherapy approach, but they gave you a choice?

Mrs. SEXTON. They told me there were other chemotherapies available, unproven, only experimental. They thought for Dwayne's best benefits that radiation should be used at that point, said we would be just losing time if they did go into more chemotherapy, time which he might need if he took radiation.

Mr. GORE. You told them to do what they thought was best?

Mrs. SEXTON. I said do what is best for Dwayne, that is what I am here for in the first place.

Mr. GORE. OK. At that point they told you that they would put him in the radiation chamber, right?

Mrs. SEXTON. Yes.

Mr. GORE. OK. Now there were two radiation chambers at the facility, is that correct?

Mrs. SEXTON. Yes, sir.

Mr. GORE. You refer in your statement to METBI and LETBI. Those of us who have been living with this issue for weeks and months are familiar with it but others may not be. METBI is medium-exposure total-body irradiation facility; LETBI is the low-exposure total-body irradiation facility.

Mrs. SEXTON. Yes, sir.

Mr. GORE. And your son was placed in the METBI or medium-exposure facility for 3 hours, 38 minutes, and given a large dose of radiation, after which he was taken upstairs to the third floor of the same building and placed in the LETBI facility, the low-exposure facility.

Now, you were quoted earlier as saying that you saw animals in the hospital during this period. Now they were not at the LETBI facility, were they, where your son was placed to recover?

Mrs. SEXTON. What they had quoted was some documents that the researchers went down and saw there. I didn't quote anything about animals. But I do know they were downstairs, down the hallway from the outpatient area. I do not know where else in the hospital they were located because I wasn't familiar with them.

Mr. GORE. Fine, fine.

Now why were you told your son was placed in the LETBI facility, the one on the third floor?

Mrs. **Sexton**. I was told he would be placed up there as a sterile environment, to keep him away from bacterial infections. But he was also placed on this belt and these readouts, they were not returned with his medical records. I mean I do not know what purpose that served because it was on him for some time and I just don't know what purpose it was for him.

Mr. **Gore**. OK. When you say he was placed on a belt——

Mrs. **Sexton**. He was laid in a bed and the belts were strapped around him.

Mr. **Gore**. What?

Mrs. **Sexton**. A belt was strapped round him to read his respiration, heartbeats, and all his vital signs.

Mr. **Gore**. OK. How long was the belt kept on Dwayne?

Mrs. **Sexton**. That I just cannot remember for sure, maybe a couple of days off and on. I do not know. I stayed in isolation with Dwayne for several days. Maybe I went out in the hall for some purpose, but I did see these readouts coming through the machinery and they did have NASA written on the machinery. I have no documents at all from that.

Mr. **Gore**. Later testimony will indicate that the machinery was paid for by NASA and that may or may not have significance. We will see later in the inquiry.

Mrs. **Sexton**. Sure, but I wonder what the readouts were, what purpose were they checking for again? I don't know what it would be for him to have these readouts on him.

Mr. **Gore**. When you say readouts, were they paper readouts?

Mrs. **Sexton**. Yes; they were on paper.

Mr. **Gore**. Printed readouts?

Mrs. **Sexton**. Yes, sir, they were.

Mr. **Gore**. All right. And then they took the belt off after what, a couple of hours?

Mrs. **Sexton**. I think it was possibly more than that, I don't know, maybe he was hooked up again. I can't remember for sure.

Mr. **Gore**. And then you took him home shortly after that?

Mrs. **Sexton**. No, sir.

Mr. **Gore**. He stayed in the hospital?

Mrs. **Sexton**. He stayed there until he died.

Mr. **Gore**. He stayed there until he died. But that was the last radiation?

Mrs. **Sexton**. He had one single dose of radiation, downstairs. Upstairs he was only put in there, they told me, for the sterile effects.

Mr. **Gore**. As far as you know, there was no radiation up there?

Mrs. **Sexton**. There shouldn't be because I stayed in the room with him during the night and day too.

Mr. **Gore**. You stayed there with him until he died?

Mrs. **Sexton**. Yes, sir, I did stay with him.

Mr. **Gore**. Mr. Walker?

Mr. **Walker**. Thank you, Mr. Chairman.

First of all, Mrs. Sexton, I want to thank you for your courage in coming here. I know it is difficult for you; it certainly is difficult for us as well.

Mrs. Sexton. Sure.

Mr. Walker. Anyone who has ever confronted cancer close up in a loved one knows you were under a tremendous strain during the period of time that your son was ill and that can't help but carry over until the present day. The chairman explained before what we are trying to do is get to the bottom of it and ask questions that will allow us to develop some understanding.

Looking through your testimony here, I want to do the same thing that the chairman did to some degree and try to get my timeframes in place here.

At one point in your testimony you are talking about the fact that you received a copy of a report just fairly recently.

Mrs. Sexton. Yes, sir.

Mr. Walker. And you said that in that report you found out there was a possible hazard to you in the transmission of the leukemia, and you say here, "The doctors never told me of that possible hazard."

Now, a little later in your statement, you talk about the fact that when the doctors were treating Dwayne there was talk of a bone marrow transfer between Dwayne and his dad.

Mrs. Sexton. Yes, sir.

Mr. Walker. And you said: "I refused because I didn't want anyone else to take the risk of being infected with leukemia cells." I am having trouble in terms of the chronology. If you didn't know about the risk until recently, what was the concern of the risk that you were referring to at that point in your statement?

Mrs. Sexton. OK. I knew what stuff I went through, all this trouble, I knew my blood pressure had dropped extremely low. I was concerned; my husband, after all, we needed some kind of moral support. Cancer is nothing to play with. You do not inject people with cancer cells no matter what. I was willing to take the chance, sure; I would do it again, but I didn't want him to be exposed to it.

One child for me to care for with cancer and watch him, no, I couldn't take no more, no one.

Mr. Walker. What you are saying is that from your own judgment, just based on your own experience, you knew there were risks involved but the first time you ever had that confirmed was when you received this report recently.

Mrs. Sexton. Sure. Dr. Edwards said there is such a remote possibility that we wouldn't even think of this—it just has never happened before.

Mr. Walker. As I say, I am tryng to find out here, no one——

Mrs. Sexton. Told me there was a possibility.

Mr. Walker. The possibility of a risk, you just assumed a risk?

Mrs. Sexton. Sure. He said there is never a possibility because it never happened before.

Mr. Walker. You said that the reason you kept Dwayne at Oak Ridge is because "we were told they had the best treatment available anywhere"?

Mrs. Sexton. Yes, sir.

Mr. Walker. Who told you that?

Mrs. Sexton. Dwayne's pediatrician, Dr. Robert Northrop, in Kingsport, told us that; Dr. Leeds told us that, and one of his assistants when he was out told me, "You are very fortunate, they have the very best." Everyone I talked to. In fact, we had access to Blue Cross, Blue Shield, major medical, from November 1965 until present. We didn't take advantage. We thought we had the best available for us.

Mr. **Walker**. How would you describe the physicians at Oak Ridge that you dealt with?

Mrs. **Sexton**. To me I thought they were extremely talented; they were good people; I trusted them.

Mr. **Walker**. So in terms of the advice you had gotten from your pediatrician and others, you felt that the treatment he was getting at the time was the——

Mrs. **Sexton**. Very best.

Mr. **Walker**. Very good treatment. Did they appear at that time to be concerned about your son's welfare?

Mrs. **Sexton**. I thought so.

Mr. **Walker**. How about the rest of the staff, the nurses, and the other people at Oak Ridge that you dealt with; would you describe them in the same terms, that they were competent, they were professional, they appeared to be concerned about your son's welfare?

Mrs. **Sexton**. I thought so at the time, because it is just like routine hospital life.

Mr. **Walker**. As you know, one of the reasons why we are looking at this so carefully is because of the charges that have been made in the article that was in Mother Jones Magazine. Did you approach the magazine once you had read this report, the report that you referred to; did you approach them with this particular story and tell them that you had concerns?

Mrs. **Sexton**. They printed a story, and I have talked to them but I have not directly—this is Mr. Rosenberg's article that he had printed. He has taken his documents and then he took a statement from me and he published the statement that I made, that I was concerned.

Mr. **Walker**. But you did not see the reports until after the article had been published, is that——

Mrs. **Sexton**. I saw the reports, that is what had me extremely upset, these documented things from NASA, Oak Ridge, and different places.

Mr. **Walker**. What I am trying to determine is, did the magazine, after they had gotten the reports, approach you? Do I understand that correctly? In other words, the magazine received the reports and at that point they approached you, showed you the reports, and then took a statement from you after you had a chance to review the reports?

Mrs. **Sexton**. Yes.

Mr. **Walker**. Do I also take from your statement that you remain completely independent from the magazine?

Mrs. **Sexton**. Sure, I still am.

Mr. **Walker**. Thank you.

Mr. **Gore**. As I understand it then, your attitude toward the people at the facility, the doctors and nurses and others, was and remained positive until you came into the posession of new information that caused you to change your attitude?

Mrs. **Sexton**. Yes, sir.

Mr. **Gore**. And that was when the reporter came and talked with you about the information?

Mrs. **Sexton**. Yes, sir, they showed me these documents. I read them myself and asked questions in my mind what has happened.

Mr. **Gore**. I understand.

Mr. Shamansky?

Mr. **Shamansky**. Thank you, Mr. Chairman.

Mrs. Sexton, to have exposed yourself to cancer cells, regardless of what condition they might have been at the time, to help your child, you must have been very, very concerned about your child's health.

Mrs. **Sexton**. I was.

Mr. **Shamansky**. How old was Dwayne when you first noticed that he was ill?

Mrs. **Sexton**. Three and a half years old.

Mr. **Shamansky**. Three and a half years old?

Mrs. **Sexton**. Yes.

Mr. **Shamansky**. And you went to your local doctor, for assistance?

Mrs. **Sexton**. Yes, sir.

Mr. **Shamansky**. To find out what kind of illness he had?

Mrs. **Sexton**. Yes, sir.

Mr. **Shamansky**. Did your physician, unrelated to anything to do with the Government, make any kind of a prediction at that time as to what the prognosis would be, what the prospects were for your boy?

Mrs. **Sexton**. He told me Dwayne had this aplastic anemia and he says if the cause wasn't found soon, and if it wasn't corrected, it could possibly turn into leukemia. That is the reason I was concerned with these experiments, I was looking for what was causing his aplastic anemia.

Mr. **Shamansky**. But at the time that you did, I assume you understood that this was a very serious matter for your child?

Mrs. **Sexton**. Of course I knew it would be.

Mr. **Shamansky**. And did they predict at all that it would be fatal to him?

Mrs. **Sexton**. No, sir. He said if the cause is found for this aplastic anemia, I was thinking Dwayne would be OK.

Mr. **Shamansky**. But they did tell you that aplastic anemia could develop into leukemia?

Mrs. **Sexton**. If the cause wasn't found, that it possibly could.

Mr. **Shamansky**. What hope did they hold out to you that they might find that cause?

Mrs. **Sexton**. Well, the physician talked to Talmon, my husband. I kept Dwayne in the car because he was extremely upset from being hospitalized. I was relieved after 4 days of just getting out. I let him go in. I thought Dwayne's problem had been found because he didn't tell me when he released him there was anything serious the matter with him.

Mr. **Shamansky**. How much time passed and what was the condition of Dwayne when you first made contact with the medical facility at Oak Ridge?

Mrs. SEXTON. Our doctors made arrangements with him. We stayed home with him one night and he was immediately admitted the next morning.

Mr. SHAMANSKY. Did you stay in touch with your pediatrician?

Mrs. SEXTON. Yes, we did.

Mr. SHAMANSKY. Did he continue to be in touch with Oak Ridge?

Mrs. SEXTON. Yes, they mailed his release forms, things like that, the times he was admitted and released, they would update him on his condition.

Mr. SHAMANSKY. Then when was the first time that you understood that Dwayne had leukemia?

Mrs. SEXTON. The following day after they did a bone marrow test on Dwayne.

Mr. SHAMANSKY. So it was a fairly short period between the time you knew about his anemia and that you then realized it was in fact leukemia?

Mrs. SEXTON. Yes, it was, about 48 hours or so.

Mr. SHAMANSKY. Forty-eight hours. At that point, once you had been told Dwayne had leukemia, was there any discussion as to the prospect how long he might live?

Mrs. SEXTON. No, sir, there was not.

Mr. SHAMANSKY. Was there any discussion that he might die?

Mrs. SEXTON. No, but I knew leukemia was fatal. I knew that myself.

Mr. SHAMANSKY. You knew at that point that your son's life was in danger.

Mrs. SEXTON. You know I did.

Mr. SHAMANSKY. Am I fair in concluding from that that is why you were willing to undergo, yourself, treatments and that you would then have your son try the same thing because you felt his life was truly in danger?

Mrs. SEXTON. Yes, sir, I did, I would have done anything for him.

Mr. SHAMANSKY. OK.

Were you ever told that this was the first time this treatment was ever done with respect to people?

Mrs. SEXTON. That was told to me that it had been proven with animals and through theory that it would work and it was promising enough for Dwayne that they thought it would be a good thing if we did go through with it.

Mr. SHAMANSKY. But there was no representation that other people had been treated that way successfully or even unsuccessfully?

Mrs. SEXTON. Not that I could——

Mr. SHAMANSKY. Not that you could remember?

Mrs. SEXTON. Possibly, 13 years is a long time to remember. I do not want to say anything is true that was not.

Mr. SHAMANSKY. But certainly you didn't meet any family that had——

Mrs. SEXTON. I never met anyone, everything was always just on a one-to-one basis.

Mr. SHAMANSKY. All right. When the treatments started, the contact with Oak Ridge started, did you continue your relationship with your own personal doctor?

Mrs. Sexton. Yes, sir. In fact, he notes in his medical records that he did. He gave him part of the treatments during times.

Mr. Shamansky. So in fact there was sort of a parallel medical surveillance—your personal doctor who was not in the employment of the Government and then the Government, the Oak Ridge doctors?

Mrs. Sexton. When he was on methyltrexate, there was during that time only, they both treated the same thing. The other things, they were not involved with them.

Mr. Shamansky. During the time that Dwayne was not at Oak Ridge, you mentioned five or six relapses. I assume that during that time your own private physician was caring for Dwayne?

Mrs. Sexton. No, sir; they was treating—they said any relapses, in his papers, medical records that was released to me, that he was in a relapse on these dates and he would go into remissions again and it is documented in Dwayne's medical records.

Mr. Shamansky. These are medical records at Oak Ridge?

Mrs. Sexton. Yes, sir, at Oak Ridge.

Mr. Shamansky. Did you consult with him to help you understand what was going on with Dwayne? During this time did you continue your relationship with your private doctor?

Mrs. Sexton. I kept taking him there and he would check him. I thought everything was as it should be.

Mr. Shamansky. But did you undersatnd the nature of what a relapse was?

Mrs. Sexton. I just knew they had gone into remission or that it had come out of remission; that is the way I understood it.

Mr. Shamansky. You do know it was an up-and-down situation?

Mrs. Sexton. Yes.

Mr. Shamansky. When there was a relapse, the boy was becoming sick again and when there was remission he was better?

Mrs. Sexton. Sure.

Mr. Shamansky. This was the pattern over approximately 3 years?

Mrs. Sexton. Yes, sir.

Mr. Shamansky. What finally happened at the last relapse, after that; there must have been something that brought this situation to your attention.

Mrs. Sexton. He just had, like any little child he had a nosebleed. They told me to be extremely careful and watch him for nosebleeds. It frightened me very much and I called him in the middle of the night and told him his nose started bleeding and just the normal things that you would do to stop a nosebleed, it couldn't get it to stop. So they said bring him in immediately. We took him back down there and they did their blood tests. It stopped a while after he was there.

Mr. Shamansky. At that point you knew he was in a relapse, he had relapsed again?

Mrs. Sexton. No, sir; I didn't know it myself. They just told me to watch him.

Mr. Shamansky. But you brought him to the hospital after he became ill in the night.

Mrs. SEXTON. We would do this any time with an infection or anything at all; they treated him. I mean anything—you want your doctor to be informed on anything, especially someone with cancer.

Mr. SHAMANSKY. At that point did they tell you this was a more serious relapse than the previous ones, after they completed their tests?

Mrs. SEXTON. After they had admitted him and run the tests again, they told us it was.

Mr. SHAMANSKY. You knew this was something different than what had gone before?

Mrs. SEXTON. I thought in my mind it was just another relapse. On this occasion they seemed to think it was even worse. I don't know; I do not know blood reports, things like that.

Mr. SHAMANSKY. At least it just wasn't routine; it was a little different than what had gone on before?

Mrs. SEXTON. Possibly.

Mr. SHAMANSKY. OK.

Did you then have contact, did you confer with your private doctor at that point?

Mrs. SEXTON. No, sir. He was just only treating him in the meantimes. We just turned his full treatments as far as that went to them, because they had treated him for infections, everything. Of course we would take him back whenever he needed it, for his appointments.

Mr. SHAMANSKY. It is a little elusive for me. Can you describe the relationship? Did Dwayne continue to see his private doctor as well as the Oak Ridge doctors?

Mrs. SEXTON. Sure, but not often like he would them. He would have no standard setup as with them, like very 2 weeks. We were there 6 or 7 weeks at a time. There was no way we could keep up to date with them because there was just a constant thing twice a week.

Mr. SHAMANSKY. At this last time, was your private doctor aware that Dwayne had a relapse and was going to be in the hospital?

Mrs. SEXTON. Possibly not, because I went down there immediately, when I found it out. I stayed 7 weeks without going home, and also there was no need for him to know until Dwayne was released.

Mr. SHAMANSKY. During that long period that you were there, did they tell you, and were you satisfied that this was a more serious situation requiring perhaps a different kind of treatment?

Mrs. SEXTON. He convinced me; I mean you trust him; I thought so from his word.

Mr. SHAMANSKY. OK. Do the medical records show that Dwayne in fact had had a more serious relapse?

Mrs. SEXTON. I have not had them documented or anything. I have them available for anyone who wants to check it. I do not know that good.

Mr. SHAMANSKY. Thank you, Mr. Chairman.

Mr. GORE. OK. Thank you.

You did sign a consent form; is that correct?

Mrs. SEXTON. Well, I do not—when I admitted him to any hospital or when anyone is admitted you sign a form saying there is risk for anything they do. But the experiments, we were looking for what was causing aplastic anemia, of course you were going to experiment; you are going through risks. I didn't think there was any more, maybe a little more than what you would do to find answers to anything.

I didn't know this was a cancer research hospital. I just knew they were trying to find out what was causing that. I was not informed even by my physician what this was.

Mr. **Gore**. Well, without objection, we will put the consent forms involved in the record.

Mrs. **Sexton**. Yes, sir, sure.

Mr. **Gore**. At this point.

[The information follows:]

Med. 13
Rev. 1 (4-57)

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES
MEDICAL DIVISION

PATIENT ADMITTANCE AGREEMENT

In consideration of my being accepted and admitted to the Research Hospital operated by the Oak Ridge Institute of Nuclear Studies, I, on behalf of myself, my heirs, executors, administrators, and assigns, covenant, understand and agree as follows:

1. To hereby release and discharge the Oak Ridge Institute of Nuclear Studies, its officers, agents, and employees from any actions, damages or claims resulting from my hospitalization in said hospital and/or any treatments and care received while in said hospital or by reason of my having been a patient therein.

2. That any treatments administered to me may be experimental.

3. That I have not been influenced in making this agreement by any representations or statements regarding improvement in my physical condition or the probable results of any treatments received, but instead expressly assume all risks incident to my hospitalization, care and treatment.

4. I understand that but for this agreement on my part, I would not be accepted and admitted as a patient in said hospital.

5. I covenant that I have carefully read the foregoing and fully understand the meaning and contents thereof, and have executed the same of my own free will and choice.

Date July 27 1965

Signed Talmon Dwayne Sexton
Patient Age 3 years

WITNESSES:

Mary E. Ratliff

Wanda E. Hodge

Talmon Sexton
Father or Guardian

Marysue Sexton
Mother

We understand and agree to a special experimental procedure designed to try to help our child who has acute leukemia. This will consist of removing bone marrow from the child, subjecting the marrow to radiation designed to kill the leukemic cells, and subsequently injecting these cells into the mother. At a later date it is planned to operate on the mother to drain lymph from the thoracic duct to obtain cells that can be injected back into the patient in an effort to combat the leukemia.

Since this is a new and experimental procedure, there are some risks involved for both mother and child. The nature of these has been explained to us and we are willing to accept them.

Our acceptance of this procedure is entirely voluntary. The staff of the Medical Division has put no pressure on us to agree to this, and has freely offered more conventional treatment as an alternative.

Talmon Sexton

Mary Sue Sexton

8-5-65

Date

Mildred V. Hentz, RN

Witness

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

I authorize the performance upon Duayne Sexton (myself or name of patient)
of the following treatment: total Body irradiation

(State nature of treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may be unpredictable.

DATE 3 Dec '68 Mary Sue Sexton (Patient or person authorized to consent for patient)

WITNESS.

I have talked with Mary Sue Sexton (Name) about
the proposed course of treatment to be given Duayne Sexton (Name)
including the following:* purpose and alternative of therapy & possible effect

C. L. Edwards (Physician) 3 Dec. '68 (Date)

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

Mr. GORE. I take it from your response that you signed it the way most people do.

Mrs. SEXTON. Sure.

Mr. GORE. This was part of getting in and you gave it a kind of a quick look and signed it?

Mrs. SEXTON. Sure.

Mr. GORE. Which doctors did you deal with during Dwayne's stay at the hospital and treatment there?

Mrs. SEXTON. There were several of them. Most of them were on exchange programs through universities, mostly with Edwards, Andrews, Vodopick, Tenita, Gengozian, and there were several technicians.

Mr. GORE. Not Dr. Lushbaugh?

Mrs. SEXTON. He was over in the radiation department, I think.

Mr. GORE. But you did not deal with him?

Mrs. SEXTON. Possibly. He should have been because he was over the treatments in radiation, he was the head of these departments. I didn't associate much with the people downstairs in their own departments, department heads, I dealt with his doctors directly one to one.

Mr. GORE. Did you remember speaking with Dr. Lushbaugh?

Mrs. SEXTON. One time in particular I was introduced to him. He was the head downstairs. And Annie Sipe was our close friend, this was her boss, Dr. Lushbaugh.

Mr. GORE. All right. Throughout the course of the hearing today, we are going to try to get some answers to the questions you have raised in your testimony, and we will also be addressing the other questions about the goals at the Oak Ridge Division.

You did not at the time feel that Dwayne was a part of anything other than a treatment procedure, did you?

Mrs. SEXTON. I thought he was there for his benefit and this radiation was for his benefit. After I found these infections were there, he was put in a sterile environment to keep him from getting infections but he was already given this large dose of radiation with this infection that you usually don't expose people to it, at least a high dose of radiation when they have already been proven they do have a bacterial infection.

Mr. GORE. We will ask that question as well.

When the belt was put on him, do you remember any question of NASA at that time?

Mrs. SEXTON. Just casually with Annie.

Mr. GORE. How do you mean casually?

Mrs. SEXTON. We sit and talk, I stayed there all these days and weeks. We would talk in the hall. I would see her through the glass operating machinery.

Mr. GORE. This is Mrs. Sipe.

Mrs. SEXTON. Yes, it is. She just casually talked to me.

Mr. GORE. And during the casual conversation she happened to mention that the equipment was——

Mrs. SEXTON. Was NASA's.

Mr. GORE. Was NASA equipment?

Mrs. SEXTON. Yes, sir, it had NASA written on it too.

Mr. GORE. OK.

How long did he stay in LETBI?

Mrs. SEXTON. He stayed there all the time from the time of his radiation exposure to, until December 29, the third from the 29th.

Mr. GORE. During all of that time the belt was attached for only the first hour, or 2 or 3 hours?

Mrs. SEXTON. I couldn't say, it may have been put off and on, I don't know, I don't know for sure. I do know it was for some little time.

Mr. GORE. To the best of your recollection, it was only the first day, is that right?

Mrs. SEXTON. Possibly so.

Mr. GORE. OK. Well, thank you very much.

Those are all the questions that we have for you. We are going to take your testimony and develop questions from it for the witnesses who will now be appearing.

Mr. SHAMANSKY. Mr. Chairman?

Mr. GORE. Mr. Shamansky.

Mr. SHAMANSKY. If I may, I am concerned about one thing, Mrs. Sexton.

Mr. GORE. Sure, go ahead.

Mr. SHAMANSKY. The questions that I was trying to ask and that I am not sure I got it clear in my own mind, on the last visit to the hospital where you went with Dwayne, were you aware that he was really quite sick at that point?

Mrs. SEXTON. Not until after they told me that he was.

Mr. SHAMANSKY. But he was sick enough that you went with him to the hospital and after you got to the hospital did they tell you that he was really quite sick at that point?

Mrs. SEXTON. The main thing I went there was because of the nosebleed they had told me to be watching for. When you have someone with leukemia you knew it is extremely frightening, because their platelets drop so low.

Mr. SHAMANSKY. So you took him in?

Mrs. SEXTON. Sure.

Mr. SHAMANSKY. Then they did some tests on him?

Mrs. SEXTON. Yes.

Mr. SHAMANSKY. At that point—did they inform you that he was really quite sick at that point?

Mrs. SEXTON. He said he was in a precarious position, he said he had infections, his blood counts were depressed.

Mr. SHAMANSKY. And that was probably the worst description, was that in fact as bad a description of his condition as you had had up until then, as to what condition he was in?

Mrs. SEXTON. No, sir, I do not think so, because he had staph pneumonia before, he was depressed very much. He has had remissions. He would get so low that this was not really shocking. When you go all these years and see things happen, it is nothing.

Mr. SHAMANSKY. But they did the experiments and the tests and determined he was in a serious condition?

Mrs. SEXTON. That is what I went by.

Mr. SHAMANSKY. Right. And they confirmed after their tests that he was quite seriously ill?

Mrs. SEXTON. Yes, sir, that is how I took it.

Mr. SHAMANSKY. Did they discuss with you their estimate of how long he had to live?

Mrs. **SEXTON**. They did not. They said if he wasn't treated with some means that he would not live long. Anyone would undersatnd that.

Mr. **SHAMANSKY**. And did they tell you what treatments were available to someone in that condition at that point?

Mrs. **SEXTON**. Yes. They said there is either three types, you can use blood transfusions, we know that is just prolonging, maybe weeks, whatever; they told me there was unproven experimental drugs. They said if we put him on that possibly we would not get much responses and would just be wasting time because they did have radiation they thought it was promising enough, that is what they thought Dwayne should be treated with.

Mr. **SHAMANSKY**. It was on the basis of that that you made a choice as to the types of treatment?

Mrs. **SEXTON**. I said you know what you have to treat with, the responses you are going to have with it, I said I think your judgment is better than mine what to treat him with.

Mr. **SHAMANSKY**. Was there any reference by the medical authorities there that this experimental treatment had or had not in fact ever been used on a human being before?

Mrs. **SEXTON**. That is why I say, I cannot remember directly for sure, but to my knowledge possibly it had somewhere else, because—

Mr. **SHAMANSKY**. But as far as you can remember, there was no reference to the fact by them that it had ever been used on a human being?

Mrs. **SEXTON**. That is the way I understood it.

Mr. **SHAMANSKY**. Not as you understand it, but as you remember it is what I am trying to say.

Mrs. **SEXTON**. Yes, sir.

Mr. **SHAMANSKY**. You don't remember their saying it had been used on anybody before? It is a long time, I am not trying to put words in your mouth.

Mrs. **SEXTON**. That is the reason I don't want to make a statement.

Mr. **SHAMANSKY**. In other words, you don't remember one way or the other?

Mrs. **SEXTON**. No, not quite clearly, that is the reason I don't want to say yes or no.

Mr. **SHAMANSKY**. Did any of the medical staff ever discuss the risks involved at that point?

Mrs. **SEXTON**. I thought it was indepth risks, but then I have seen his paper shows there was people that had been exposed through kidney-graph, when their immune system had been doctored, whatever it would be, they couldn't fight bacteria or anything like that; like he was going to have a transplant, they knock it down. Then they can give cancer with it, like a kidney-graph.

My system had been knocked down by the removal of antibodies from me. So there was a very great possibility that I would have taken this leukemia, and still a possibility after these years, even up to 20 years that there is a very great possibility that it—

Mr. **SHAMANSKY**. Was there any indication from the medical staff that any hospitals in the reasonable vicinity, say in the state, had done anything like this or had a better cure rate, whatever that cure rate was?

Mrs. **Sexton**. No, sir, there was nothing better that I thought of.

Mr. **Shamansky**. OK. Thank you very much.

Mr. **Gore**. Thank you, Mrs. Sexton.

Ms. **Tucker**. Mr. Chairman, there is an attachment to Mrs. Sexton's statement with the citation to a scientific journal article that appeared in Cancer in 1975, and we would like to have this appear in the record.

Mr. **Gore**. Yes, we intended to put that in the record anyway. Without objection that will be included in the record.

Ms. **Tucker**. Fine.

Mr. **Gore**. At the conclusion of our questioning of Mrs. Sexton.

Thank you very much, and we will try to develop some answers for the questions that you have raised. Thank you. Thank you for your courage.

[The attachment mentioned above follows:]

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES
MEDICAL DIVISION

PATIENT ADMITTANCE AGREEMENT

In consideration of my being accepted and admitted to the Research Hospital operated by the Oak Ridge Institute of Nuclear Studies, I, on behalf of myself, my heirs, executors, administrators, and assigns, convenant, understand and agree as follows:

1. To hereby release and discharge the Oak Ridge Institute of Nuclear Studies, its officers, agents, and employees from any actions, damages or claims resulting from my hospitalization in said hospital and/or any treatments and care received while in said hospital or by reason of my having been a patient therein.

2. That any treatments administered to me may be experimental.

3. That I have not been influenced in making this agreement by any representations or statements regarding improvement in my physical condition or the probable results of any treatments received, but instead expressly assume all risks incident to my hospitalization, care and treatment.

4. I understand that but for this agreement on my part, I would not be accepted and admitted as a patient in said hospital.

5. I covenant that I have carefully read the foregoing and fully understand the meaning and contents thereof, and have executed the same of my own free will and choice.

Date 11 December 1959

Signed ____________________
Patient

WITNESSES:

Mary E. Pittsley

Dorothy L. Vela

____
Father or Guardian

____
Mother

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES
MEDICAL DIVISION

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In consideration of my being accepted and admitted to the Research Hospital operated by the Oak Ridge Institute of Nuclear Studies, I, on behalf of myself, my heirs, executors, administrators, and assigns, covenant, understand and agree as follows:

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3. That I have not been influenced in making this agreement by any representations or statements regarding improvement in my physical condition or the probable results of any treatments received, but instead expressly assume all risks incident to my hospitalization, care and treatment.

4. I understand that but for this agreement on my part, I would not be accepted and admitted as a patient in said hospital.

5. I covenant that I have carefully read the foregoing and fully understand the meaning and contents thereof, and have executed the same of my own free will and choice.

Date [illegible] 1960

Signed ______________________
Patient

WITNESSES:

____

____

____
Father or Guardian

____
Mother

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

I authorize the performance upon myself
(myself or name of patient)
of the following treatment: Allogeneic bone marrow transplantation from my brother after total body irradiation and infusion of antihuman thymocyte globulin.
(State nature of treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may [illegible] unpredictable.

DATE: Aug 17, 1970
(Patient or person authorized to consent for patient)

WITNESS:

I have talked with ______________ about
Name
the proposed course of treatment to be given himself
Name
including the following:* See attached explanation

Aug 17, 197
Physician
Date

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

I UNDERSTAND AND AGREE TO A SPECIAL EXPERIMENTAL TREATMENT, BONE MARROW TRANSPLANTATION, DESIGNED TO TREAT MY DISEASE, ACUTE LEUKEMIA, BY REPLACING MY BONE MARROW WITH THAT OF MY BROTHER. THE TREATMENT WILL CONSIST OF 1) RECEIVING A NEW DRUG, HORSE ANTIHUMAN THYMOCYTE GLOBULIN, 2) 500 R OF TOTAL-BODY IRRADIATION AT THE U. T. AEC AGRICULTURAL STATION, AND 3) RECEIVING AN INFUSION OF FRESH BONE MARROW CELLS OBTAINED FROM MY BROTHER. I UNDERSTAND THAT SPECIAL PRECAUTIONS INCLUDING ISOLATION IN THE LAMINAR-AIR FLOW ROOM AND ANTIBIOTICS WILL BE USED IN AN EFFORT TO CONTROL INFECTION.

SINCE THIS IS A NEW AND EXPERIMENTAL PROCEDURE, THERE ARE RISKS INVOLVED. THESE RISKS HAVE BEEN FREELY AND OPENLY DISCUSSED WITH ME BY DRS. H. A. VODOPICK AND C. L. EDWARDS AND INCLUDE:

1) REACTION TO THE HORSE GLOBULIN

2) RADIATION ILLNESS

3) A REACTION OF THE BONE MARROW GRAFT AGAINST MY NORMAL TISSUES

FURTHER, IT HAS BEEN EXPLAINED THAT ANY OF THESE REACTIONS MAY BE VERY SERIOUS AND, IF UNCONTROLLABLE, MAY PROVE FATAL.

I ALSO UNDERSTAND THAT THE EXPERIMENTAL TREATMENT MAY PROVE INEFFECTIVE AND THAT MY DISEASE MAY RETURN PROMPTLY. SHOULD THE TREATMENT SUCCEED IN CONTROLLING THE LEUKEMIA, I MAY STILL BE MORE SUSCEPTABLE TO INFECTIONS THAN A NORMAL PERSON. NEVERTHELESS, I HAVE WEIGHED THESE RISKS AGAINST THE EXPECTANCY WITH OTHER TREATMENTS AND MY ACCEPTANCE OF THIS EXPERIMENTAL TREATMENT IS ENTIRELY VOLUNTARY AND THE STAFF OF THE ORAU MEDICAL DIVISION HAS NOT COERCED ME TO AGREE TO THIS BUT HAS FREELY OFFERED MORE CONVENTIONAL TREATMENT AS AN ALTERNATIVE.

Mrs.	
WITNESS	SIGNATURE
C. Lowell Edwards Jr.	Aug 17, 1970
WITNESS	DATE

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

I authorize the performance upon Myself (myself or name of patient) of the following treatment: Total body irradiation in the Low exposure rate facility. The total dose will be 150 Roentgen. (State nature of treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may be unpredictable.

DATE: January 29, 1973 ____________ (Patient or person authorized to consent for patient)

WITNESS: ____________

I have talked with ____________ (Name) about the proposed course of treatment to be given TBI, LETBI (Name) including the following:* purpose and therapeutic and other consequences.

Karl F. Hubner (Physician) Jan 29, 1973 (Date)

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

I too have discussed these with patient

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

Authorization for the Administration of Radioactive Substance

I hereby authorize the staff of the ORINS Medical Division to

administer to ______________________________ the following radio-

active substance ____________________ ______________________________
Nuclide Chemical

____________________________ ______________________________.
Dose Route of administration

The purpose of this procedure has been explained to me as being:

____

____

____

Its relevance to my condition, the risks and any possible alternatives have been explained to me.

____
Name of patient

____
Date

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Patient Admittance Agreement

The Oak Ridge Institute of Nuclear Studies (ORINS) Medical Research Hospital is operated by Oak Ridge Associated Universities (ORAU) for the U. S. Atomic Energy Commission (AEC) for the conduct of certain clinical research programs. These programs are mainly in areas allied to the application of radiation and radioisotopes to medicine and other health sciences.

I understand that I have been accepted as a patient for admission to the hospital, or as an outpatient, because my physical condition has been determined by the hospital staff to make me a suitable patient for a currently active clinical research project.

I further understand that while a patient at the research hospital examinations, treatments, and tests may be prescribed which are experimental in nature and I hereby consent to such examinations, treatments, or tests. Notwithstanding the above, I reserve the right to a full explanation of any such proposed examination, test, or treatment and the right to withdraw my consent. I further reserve the right to withdraw completely should I find that I am unable to continue.

I further understand that I can remain in the research hospital only so long as I am needed for research purposes, and that I must be discharged when my participation in a study is completed and when, in the opinion of the hospital staff, my medical condition permits. In such event, I understand that ORAU, its officers, employees, and agents, cannot assume responsibility for any continued medical care.

The above statements have been explained to me by the member of the Medical Division staff named below. I understand and accept the statements.

I have not been influenced in making this agreement by any representations or statements regarding improvement in my physical condition or the probable results of any treatments received, but instead expressly assume all risks incident to my hospitalization, care, and treatment.

Patient's signature	Medical Division staff member's signature
Parent or guardian's signature	Date

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

I authorize the performance upon ______________________________
(myself or name of patient)
of the following treatment: ______________________________

____

____
(State nature of treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may be unpredictable.

DATE: ____________________ ______________________________
(Patient or person authorized to consent for patient)

WITNESS: ______________________________

____

I have talked with ______________________________ about
Name
the proposed course of treatment to be given ____________________
Name
including the following:* ______________________________

____

______________________________ ____________
Physician Date

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Operation

PATIENT____AGE______

DATE_________________________TIME__________A.M. P.M. PLACE____________

1. I hereby authorize the medical staff of the ORINS Medical Division, or such physician as they may designate, to perform upon ________________________________ (state name of patient or myself) the following operation:____.

   If in the course of the operation any unforeseen condition arises calling for procedures in addition to or different from those now authorized, I further request and authorize him to do whatever he deems advisable.

2. The nature and purpose of the operation, possible alternative methods of treatment, the risks involved, and the possibility of complications have been fully explained to me, I acknowledge that no guarantee or assurance has been made as to the results that may be obtained.

3. I consent to the administration of anesthesia by or under the direction of a staff member of the ORINS Medical Division or such other qualified person as he may designate. I further consent to the use of such anesthetics as he may deem advisable with the exception of __________________________ (if none, so state).

4. I consent to the disposal by authorities of the ORINS Medical Division of any tissues or parts which may be removed.

5. I consent to the taking and publication of any photographs in the course of this operation for the purpose of advancing medical education and science.

6. For the purpose of advancing medical education and science, I also consent to the admittance of observers to the operating room.

I CERTIFY THAT I HAVE READ AND FULLY UNDERSTAND THE FOREGOING CONSENT TO OPERATION, THAT THE EXPLANATIONS THEREIN REFERRED TO WERE MADE, AND THAT ALL BLANKS OR STATEMENTS REQUIRING INSERTION OR COMPLETION WERE FILLED IN AND INAPPLICABLE PARAGRAPHS, IF ANY, WERE STRICKEN BEFORE I SIGNED.

Signature of Patient______________________________

Signature of Patient's Spouse______________________________

When the patient is a minor or incompetent to give consent:

Signature of person authorized to give consent ______________________________

Relationship to Patient ______________________________

WITNESS:______________________________

Mr. **Gore**. I would like to call now Dr. Robert Heyssel.

Dr. Heyssel is executive vice president and director of Johns Hopkins Hospital.

Doctor, if you would raise your right hand, you swear the testimony you are about to give will be the truth, the whole truth, and nothing but the truth, so help you God?

Dr. **Heyssel**. I do.

Mr. **Gore**. Thank you very much.

Dr. Heyssel, you are uniquely qualified to present evidence to this subcommittee with respect to the questions involved because in 1967, when you were at Vanderbilt University, you established the first Human Use Committee at the Oak Ridge Medical Division. You then went to Johns Hopkins and several years later you served on the Medical Program Review Committee at Oak Ridge from 1970 through 1973, and during that period of time you were the chairman of a review of the radiation experiments at Oak Ridge, which review was specifically designed to inquire into whether or not the therapy goals had been compromised by the data acquisition goals; is that correct?

TESTIMONY OF DR. ROBERT HEYSSEL, EXECUTIVE VICE PRESIDENT AND DIRECTOR, JOHNS HOPKINS HOSPITAL

Dr. **Heyssel**. That is correct.

Mr. **Gore**. Now do you have a prepared statement?

Dr. **Heyssel**. I do not, Congressman Gore. I would like to make a preparatory statement.

Mr. **Gore**. Fine.

Dr. **Heyssel**. Which is that it has been 10 years since the events occurred about which I am to testify.

Mr. **Gore**. Yes.

Dr. **Heyssel**. When I was called about this I had almost forgotten that I had participated certainly in the Human Uses Committee. I of course remembered going to Oak Ridge several times on the advisory committee. In any event, I had no record at that time of my participation. They were subsequently sent to me from the files of Oak Ridge, and I want to be sure everyone understands I am not a reluctant witness but I may be a very forgetful one about absolute details, and I am working from really summary documents at that time.

Mr. **Gore**. I understand. That is not hard to understand at all.

Now the Human Use Committee, which was established in 1967, was designed to address the ethical questions surrounding human experimentation, is that correct?

Dr. **Heyssel**. That is correct.

Mr. **Gore**. Were such committees commonplace in the medical community at that time?

Dr. **Heyssel**. They were not commonplace. They were beginning in many places in response to concerns about drug testing, coming primarily from the FDA. I think it was about that time that institutional review boards began to be established. I should say that in the climate of those times, in thinking about this a little bit, that many things were done with human subjects, including the investigator himself, which would no longer be condoned.

When I was a—if I can put a little historical perspective on this—a house officer at Washington University Barnes Hospital in St. Louis, two of the most prominent and subsequently very prominent people in American medicine administered serum from patients to themselves who had bleeding disorders, both of them developed bleeding disorders, one of them almost died.

I cared for another investigator who was immunizing himself against white cells when I was a house officer and he almost died from that. I, myself, used radioactive labels and platelets, doing it first on myself, then on volunteer medical students.

None of those activities had to be reviewed by anyone else in any formal sense within the institutions. I think that was the situation probably up to and around 1966 in most institutions. I am not suggesting that that was the proper thing; I am simply saying that was the case.

In terms of experimental therapeutics, I think an honest effort was made by most investigators to explain to families, to patients, that what was being done was in the range of the untried or experimental, but there were certainly no informed-consent rules that anyone was operating under during that period of time up to the midsixties.

Mr. GORE. So it is fair to say that up until the midsixties the attitude toward human experimentation was very different from the attitude which now prevails?

Dr. HEYSSEL. That is correct.

Mr. GORE. But shortly after the middle sixties the medical community began to experience a greater concern about the ethical questions involved and institutions began to put into place a formal review mechanism to address those questions and to make certain that they got some attention and the Human Use Committee established at Oak Ridge was one of the first. It was not the first, as there were others, but at the time it was set up they were not commonplace?

Dr. HEYSSEL. That is correct.

Mr. GORE. Now, how did you get involved in this?

Dr. HEYSSEL. I was at Vanderbilt, I was director of the radioisotope laboratory there, a hematologist practicing, doing research, teaching. I had received training as a practical matter in the use of isotopes at Oak Ridge National Laboratories in I think 1959 or 1960. I had collaborated in research with people from Oak Ridge, Oak Ridge Institute of Nuclear Studies and the Oak Ridge Associated Universities.

I had been there for symposia, I knew them well, I was close by, relatively speaking, in a university, had had some experience at that time with the questions of human experimentation because Vanderbilt was examining that problem and beginning to develop effective review of experimentation. I was simply asked to come and advise, and asked if I would participate in that committee as an outside, supposedly, objective observer of what they were doing.

Mr. GORE. I would ask unanimous consent to put into the record at this point the minutes of a meeting held "to consider establishment of a Committee on Human Use," April 6, 1967.

[The information follows:]

Report of Meeting to Consider Establishment of Committee on Human Use

April 6, 1967

Present: Dr. Robert Heyssel, Dr. Robert Lange, Dr. Lowell Edwards, and
Dr. Gould Andrews

A meeting was held at the Medical Division on April 6, 1967, to discuss the establishment of a committee on clinical investigation which would serve to advise and monitor the Medical Division program in relation to the ethics of research in human beings and the suitability, from this viewpoint, of research going on at the Medical Division. It was pointed out that this committee would be a replacement for more informal arrangements that had previously existed in the Medical Division. The desire to have two outside consultants - Dr. Lange and Dr. Heyssel - had been stimulated by a suggestion from the Atomic Energy Commission which followed the meeting of their Advisory Committee in November, 1966. It had been pointed out by the Advisory Committee and the Commission that they did not wish to imply any criticism of our past practices, but that because of the widespread concern over ethics of human experimentation, and the possibility that some criticism, either valid or not, might arise, they believed it would be desirable to have some outside, disinterested consultants who were familiar with what we were doing, and who had passed on each individual research proposal.

A rather general discussion was held. We considered at some length the function of the committee. It was our opinion that the committee would serve to review research proposals and decide whether or not they were justifiable from the viewpoint of any risk that might be involved in studies done on human beings. If no risk is involved, the committee would not make any effort to evaluate the research proposal from the point of view of its scientific value. However, if there are significant hazards, the committee would need to evaluate the scientific merit of the proposal and balance it against the possible risks.

Name of the Committee

We chose the title, "Committee on Human Studies."

a. Composition of the Committee

It was decided to have, in addition to Dr. Lange and Dr. Heyssel, three members of the Medical Division staff on the committee. These would probably include one Ph.D. and two M.D.s. Andrews would be one of the Medical Division members and Edwards would sit in on the meetings without being an active member of the committee. We discussed at some length the fact that the people from the Medical Division would probably be involved to some degree with any research that was under consideration, and decided that in spite of this possible problem the proposed composition of the committee would be satisfactory.

b. Officers of the Committee

The committee would need a chairman, who would probably be from the Medical Division, and a secretary who would be one of the consultants. Dr. Lange has agreed to serve as secretary for at least an initial period.

Decisions of the Committee

It was our consensus that the decisions of the committee would probably need to be unanimous to allow a research proposal to go forward, or at least to have the approval of both of the outside consultants. In the event that one consultant objects to a research proposal, if there is otherwise considerable support for it, other consultation would be sought. It is our impression that in most instances the committee would be able to reach an essentially unanimous opinion on each research proposal.

Relation of the Committee on Human Studies to the Existing Radioisotope Committee at ORAU Medical Division

It was our opinion that the new committee would not replace the existing radioisotope committee. Proposed studies involving radioisotopes would need to be approved first by the ORAU Isotopes Committee and then by the Committee on Human Studies. Minor changes in research involving radioisotopes could be approved by the Isotopes Committee without further ratification by the Committee on Human Studies. Copies of the minutes of the Isotopes Committee will be sent to Dr. Lange and Dr. Heyssel.

Function of the Committee on Human Studies

The Committee on Human Studies would have meetings called by the chairman at whatever frequency seemed necessary - perhaps two or three times per year. Certain problems not requiring a full meeting of the committee could be handled by telephone communications, preferably by a three-way hook-up with Dr. Lange and Dr. Heyssel. New research proposals would be written up by the senior investigator. A form for this was developed, based upon the one used at the University of Tennessee in Knoxville with suitable modifications. After the form is filled out, the proposal will be evaluated by the administrative office of ORAU Medical Division.

If approved by the chairman of the Medical Division, or considered worthy of serious consideration by the Committee on Human Studies, copies will be sent to Dr. Lange, Dr. Heyssel, and other members of the committee previous to the meeting of the committee. At the time of the meeting, further questions may be asked of the investigator and then the committee will either approve or disapprove the research proposal.

What is to be Considered by the Committee?

The committee is to review all research at the ORAU Medical Division involving human patients in which there is believed to be a significant risk to the patients or a significant possibility that criticism might be leveled at the scientists for their manner of doing studies in human beings. The decision about whether or not a specific investigative procedure involves any risk and therefore requires action by the committee would rest with the Medical Division. The Medical Division should bring to the committee's attention by name and brief description those experiments in human beings believed to have negligible risk, i.e., a systematic survey of hemoglobin and hematocrit values in thyroid patients. Considerable discussion was held about the suitability of undertaking a rather unconventional form of treatment in a single seriously ill patient, partly with the objective of immediate benefit to the patient and partly as a preliminary research effort that might be the basis for a future controlled investigation. Here the group felt that considerable leeway rests with the physician who is responsible for the patient's care. Ordinarily the Committee on Human Studies would not be involved with decisions concerning a single patient but rather with policy matters or research on groups of patients. However, if circumstances were such that the staff of the

Medical Division wanted some consultation on the suitability of a study in an individual patient it might be quite reasonable to seek telephone discussion on this.

Scope of the Committee's Work:

It was decided that the committee should concern itself with all studies done in human beings, whether these subjects are patients in the research hospital or normal volunteers of some type.

Approval of the Previously Prepared ORAU Medical Division Document on Human Volunteers and the Function of the ORAU Isotopes Committee:

Dr. Lange and Dr. Heyssel are in agreement with the document as presented. It was pointed out by Dr. Heyssel that there are certainly some risks in using employees, and that careful protection should be given to employees used as research subjects. Students are quite unsuitable for most research procedures unless the risk is nil since they are not really free to refuse to participate. Dr. Heyssel has serious reservations about using prisoners in research because here too it is very difficult to establish a situation which is free of any suggestion of coercion.

Future Meetings:

It was decided that we would try to have another meeting, perhaps in May or June, and begin to review research proposals. We decided that we should eventually review all of the significant human research at the Medical Division, including those projects that are already under way, with highest priority to review of any studies that might be of questionable suitability or subject to criticism.

Gould Andrews
Acting Secretary

Mr. GORE. You were present at that meeting along with Dr. Gould Andrews, Dr. Robert Lang, and Dr. Lowell Edwards?

Dr. HEYSSEL. Yes.

Mr. GORE. This committee then was established in 1967?

Dr. HEYSSEL. That is correct.

Mr. GORE. This was a year prior to the irradiation of Dwayne Sexton but 2 years after the experimental immunotherapy conducted on Dwayne Sexton. Now, you did not conduct a retrospective review of human experiments at that time with the human use committee?

Dr. HEYSSEL. No, sir.

The meeting, according to the minutes I have and that is the way I remember it, was simply to establish the principles of how such a committee would be to set up, not to look back or even review what was happening at that time.

Mr. GORE. Now, how were the members of the human use committee selected?

Dr. HEYSSEL. I do not know, sir.

Mr. GORE. All right. How often did it meet?

Dr. HEYSSEL. I do not think, sir, that I met or the committee met at least with me as a participant again after that. How often the committee met and so forth, I can't say. I do not remember another meeting that I was personally involved in of this particular committee. And within a year's time I should say I left Vanderbilt to go to Hopkins, and therefore was no longer associated with it. So I can't remember if there were other meetings; I have no minutes to say that there were.

Mr. GORE. All right, fine.

Dr. Hubner, one of our later witnesses, will be able to answer some of the questions related to that, because he was a member of that committee.

Now it is my understanding that the initial determination of whether patients were at risk was made by the medical division and then those patients so designated were reviewed by the human use committee; is that your understanding?

Dr. HEYSSEL. That was my understanding of the process to be followed from minutes, yes, sir. What actually happened I do not know.

Mr. GORE. All right. Now I would like you to take that hat off and put your other hat on.

You set up the human use committee. Then you went to Johns Hopkins. Then you renewed your association with the medical division in 1970?

Dr. HEYSSEL. Yes, sir.

Mr. GORE. As a member of the medical program review committee.

Now, at that time, or rather in 1971, events occurred at another institution, the University of Cincinnati, which raised serious ethical questions about the irradiation of normal subjects.

Excuse me. Serious questions were raised about the irradiation of human beings and experiments by Dr. Eugene Sanger at the University of Cincinatti.

Dr. HEYSSEL. That is correct.

Mr. **Gore**. The funding for that program was provided by the Department of Defense and the funding was coterminous with the program of experimentation. The fact that those questions were raised elsewhere helped you, as a member of the Medical Program Review Committee, to address similar concerns at Oak Ridge because of the fact that NASA was providing funding for experiments at Oak Ridge, is that correct?

Dr. **Heyssel**. That is correct.

Mr. **Gore**. At that time you and the other members of the Medical Program Review Committee conducted a review of the ethical questions involved with the funding by NASA of a portion of the experimentation at Oak Ridge, is that correct?

Dr. **Heyssel**. That is correct.

Mr. **Gore**. Now, what was your conclusion from that review?

Dr. **Heyssel**. The conclusion was that the patients were being treated appropriately given the nature of the disease, and the status of the art of treatment of that disease in 1971-72, that information that was gained that would be useful in terms of the effects of chronic low-dose exposure over a period of time was simply a byproduct of treatment which was not all that unusual, but which was worth trying.

We did not believe at that time, and I do not today, incidentally, that what was being done was unethical, was not in the interest of the patient. The fact that other information flowed from the treatment was incidental to that.

Mr. **Gore**. At the time you conducted that review, a paper had been published by the persons responsible for the irradiation program in 1970. Were you familiar with that publication?

Dr. **Heyssel**. I might well have been; I do not remember it specifically. I have a feeling that it was probably a part of the review but I really honestly don't remember, Congressman Gore.

Mr. **Gore**. All right. Without objection we will put this in the record at this point. It is dated December 1970 and the participants in this are quite familiar with this publication. Let me just read to you what they said about the setting up of the plan and we will delve into this a little later also:

> It was not our plan to evaluate the long-range effectiveness of these relatively large individual doses of total body irradiation as a repetitive and sole therapy. This would have required establishing a total treatment plan with this technique, which we were not prepared to do.

They go on to say:

> One should not infer from this study that we expected these individual or infrequently given exposures to produce better clinical results than fractionated total body or portal irradiation. At present we feel some pattern of fractionated exposure probably offers a preferable approach.

Now was that your understanding of the nature of the experimental program at the time you conducted the review?

[The paper mentioned above follows:]

ORAU-112

HEMATOLOGIC AND THERAPEUTIC EFFECTS OF TOTAL-BODY IRRADIATION (50 R TO 100 R) IN PATIENTS WITH MALIGNANT LYMPHOMA, CHRONIC LYMPHOCYTIC AND GRANULOCYTIC LEUKEMIAS, AND POLYCYTHEMIA VERA

Mr
Escocina
Rua iRIDO
CBANIA
'61 71 88-3153

December 1970

Medical Division
Oak Ridge Associated Universities, Incorporated
Oak Ridge, Tennessee

UNITED STATES ATOMIC ENERGY COMMISSION · DIVISION OF TECHNICAL INFORMATION

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ORAU-112
BIOLOGY AND MEDICINE
(TID-4500)

HEMATOLOGIC AND THERAPEUTIC EFFECTS OF TOTAL-BODY IRRADIATION (50 R–100 R) IN PATIENTS WITH MALIGNANT LYMPHOMA, CHRONIC LYMPHOCYTIC AND GRANULOCYTIC LEUKEMIAS, AND POLYCYTHEMIA VERA*

G. A. Andrews, F. V. Comas, C. L. Edwards, R. M. Kniseley,
C. C. Lushbaugh, and Helen Vodopick

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* *From the Medical Division, Oak Ridge Associated Universities, under contract with the U. S. Atomic Energy Commission.*

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Hematologic and Therapeutic Effects of Total-Body Irradiation (50 R - 100 R) in Patients with Malignant Lymphoma, Chronic Lymphocytic and Granulocytic Leukemias, and Polycythemia Vera*

G. A. Andrews, F. V. Comas, C. L. Edwards,
R. M. Kniseley, C. C. Lushbaugh, and Helen
Vodopick

Introduction

Since 1957 the staff of the Medical Division of Oak Ridge Associated Universities has been studying the hematologic and clinical courses of patients receiving total-body irradiation. In an early experiment the radiation therapy was done in connection with attempts to graft bone marrow (1). We also have studied intensively the hematologic courses of victims of accidental exposure to radiation (2-7). The present report covers the therapeutic and hematologic results of a ten-year study — 1959 through 1968 — of single exposures of 50 R and 100 R given at approximately 1.5 R/min in a specially designed facility for total-body radiation therapy. Some of the data from this series have been published previously in brief form (8).

This study was initiated with two principal objectives; the first was to seek information that might lead to improved radiation therapy for disseminated malignant disease, especially leukemia and lymphoma, by determining the best criteria for selection of patients, radiation dose, and dose rate. For many years radiotherapists have been able to control progression of certain hematologic disorders by giving "spray X-irradiation" and have obtained similar effects using internally administered radiation, in particular phosphorus-32 (9). Fractionation and dose protraction quite logically have been used to reduce the incidence of undesirable side effects and are believed also to decrease the damage to normal tissues more than to malignant ones. However, differences in fractionation, energy of the beams, and uniformity of exposures to different parts of the body make it difficult to evaluate and compare the effects of various radiation-exposure patterns used in such therapy.

The second objective was to acquire radiobiologic information. The radiobiologic aspects of total-body irradiation on man have been studied clinically since Walsh (10) first described radiation sickness in 1897. The dose-response relationships, however, are still poorly known and present estimates are based largely on conjectures and extrapolations from animal experiments, or from experience with accident victims, atom bomb casualties, and patients treated by irradiation. Because patients in the past ordinarily have been treated with divided doses, it has been difficult to compare biologic effects in the many clinical series with each other, or with the effects seen after radiation accidents.

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* From the Medical Division, Oak Ridge Associated Universities, under contract with the U. S. Atomic Energy Commission.

We decided to obtain baseline data by giving individual doses of 50 or 100 R and then observing the patients long enough to evaluate effects. These single doses of radiation, somewhat higher than individual doses in a fractionated regimen, would provide a response that could be measured with a clear temporal relation to the date of irradiation. In contrast, an effect gradually induced by two or more variably spaced small doses would be more difficult to analyze and compare among groups of patients. Single exposures also would permit us to compare the hematologic responses with those of accident victims who usually receive single rapid exposures. Careful definitions of the effects of 50 R and 100 R, as attempted in this paper, are a necessary basis for later evaluating the effect of fractionation.

It was not our plan to evaluate the long-range effectiveness of these relatively large individual doses of total-body irradiation as a repetitive and sole therapy. This would have required establishing a total treatment plan with this technique, which we were not prepared to do. The larger doses provide a less continuous control, a possible disadvantage emphasized by Osgood. We wanted to be able to add or substitute other forms of treatment when specific clinical considerations seemed to indicate them. One should not infer from this study that we expected these individual or infrequently given exposures to produce better clinical results than fractionated total-body or portal irradiation. At present we feel that some pattern of fractionated exposure, such as that of R. E. Johnson (11), probably offers a preferable approach for total-body radiotherapy. The data reported here, by defining the range of clinical and hematologic effects that single exposures of 50 and 100 R can be expected to produce in these diseases, should provide a yardstick for comparisons in future total-body irradiation trials using different exposure patterns.

Such information, even though obtained in the abnormal conditions of disease, is helpful for assessing levels of accidental gamma and neutron irradiation injury and guiding therapeutic efforts. During the course of the study the urgent need arose for information on hematologic effects in man, since the National Aeronautics and Space Administration was faced with potentially high levels of radiation exposures in space exploration. The principal answers we sought were the pattern of responses for leukocytes, red blood cells, and platelets in chronic lymphocytic leukemia, lymphoma, chronic granulocytic leukemia, and polycythemia rubra vera. What differences occurred in response to 50-R and 100-R exposures? Did normal blood cells differ in radiosensitivity from their counterparts in proliferative disorders? For example, do platelets have a different radiosensitivity in chronic lymphocytic leukemia or lymphoma compared with polycythemia rubra vera? Or, do "normal" lymphocytes of polycythemia rubra vera have the same sensitivity as lymphocytes of chronic lymphocytic leukemia? We also wanted to observe the degree and length of clinical improvement as manifested by relief of general symptoms, and regression of masses, lymph nodes, liver, and spleen. In addition, we wanted to determine the incidence and analyze the nature of the unpleasant symptoms of acute radiation exposure which are included in another study (12).

This report completes one phase of our total-body irradiation study program. In brief this study will: 1) provide baselines for the study of fractionation effects, 2) be simpler to analyze than more complex regimens, 3) provide information relevant to radiation injury in "normal" humans. It will not: 1) demonstrate that 50 or 100 R is better than the currently accepted fractionation modes, or 2) analyze the long-range therapeutic effectiveness of these doses.

Materials and Methods

69 Patients

Patients - A total of 89 treatments were given. This report covers information on 29 exposures to 50 R, and 55 to 100 R. The remaining five were dropped from the protocols because of an urgent need for additional or different therapy before the study was finished, or because of the patient's inability to meet the appointments for follow-up outpatient visits during the study period. The number exposed and their disease categories are listed in Table 1, along with the abbreviations used in the text.

All patients with these diseases admitted to the Medical Division hospital during this period were considered for this therapeutic program. The diagnoses were established by clinical history, physical examination, and microscopic study of surgical biopsies, bone marrow, and peripheral blood samples. The urgency for treatment was assessed, and those patients whose condition required some other kind of therapy, or no therapy at all, were omitted. If the clinical status was changing rapidly and we anticipated that other additional treatment might be needed during the postirradiation observation period, these patients were also excluded. If no clearly superior therapy was available for a particular patient and the total-body radiation treatment was regarded as an acceptable way of management, the patient was offered this form of treatment, following an explanation of the research protocol. Informed consent was obtained in accordance with ethical practice to protect the rights of the individual as a research subject. We recognize some bias in the selection of one of the two doses. In a concern for the patient's safety early in the study we evaluated only the results of 50-R exposures before using the higher dose. Later, some of the patients selected for the 100-R exposure were those with more pronounced symptoms, or in lymphoma, had tumor masses that were judged to need the more vigorous treatment. On reviewing histories and clinical status,* however, we believe that these biases are not sufficiently great to prevent us from comparing a 50-R group with a 100-R group. Other forms of treatment for the disease were discontinued before the irradiation, except that in a few patients who required it, maintenance steroid therapy was kept up (see Tables D and E in Appendix). Of the patients with chronic lymphocytic leukemia, blood transfusions were given during the six-week posttreatment period (Table 2) to three exposed to 50 R and four patients exposed to 100 R. No other treatments were given during this time.

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* Summaries of clinical histories and status changes of the individual patients have been collated and included in the Appendix of this report.

Table 1

Patients Exposed to Total-Body Radiation in Each of the Disease Categories

	50 R			100 R		
	1st R_x	2nd R_x	Total R_x	1st R_x	2nd R_x	Total
Chronic Lymphocytic Leukemia (CLL)	12	3	15	16	4	20
Malignant Lymphoma	5	0	5	17	5	22
Hodgkin's Disease	1	0	1	1	0	1
Chronic Granulocytic Leukemia (CGL)	6	2	8	4	0	4
Polycythemia Rubra Vera (PRV)	0	0	0	7*	1	8
Total	24		29	45		55

*One patient had primary hemorrhagic thrombocythemia rather than PRV.

Hodgkin's disease was originally included in the study but was eliminated early because we believed that a larger dose is needed to control the malignant process than we could safely give to the whole body at one time. The most effective modern therapy for this disease is irradiation of lymphatic tissues, sometimes involving large fields, but allowing some hematopoietic tissue to remain unirradiated. The lesions of this disease are generally less radiosensitive and less intimately involved in hematopoietic tissue than those that can be helped by total-body irradiation.

Study Protocol - A uniform study protocol was devised to collect laboratory data on specified days during the six-week study period (Table 3). The six-week period of data collection was adopted as the most reasonable compromise between clinical research objectives and patient's needs; a longer period would

Table 2

The Requirement for Blood Transfusions in Patients with Chronic Lymphocytic Leukemia Before and After Radiotherapy with 50 R and 100 R TBI

		Transfusions during 6 weeks pretreatment		Transfusions during 6 weeks posttreatment	
Radiation Dose	No. Patients	No. Patients	No. Trans.	No. Patients	No. Trans.
50 R	13	3	18	3	15
100 R	8	3	15	4	31

have been clinically more desirable, and most of the patients continued under our care and had further observations. Because of the enormous spread of initial blood values, all results were normalized by using the immediate pretreatment values for each patient as 100%. In most instances, this value consisted of the average of day minus three and day zero (pretreatment) counts; in a few only day zero values were available. Table 4 gives the ranges and geometric means of the pretreatment data from which the normalized curves were derived.

Table 3

Protocol for Blood and Bone-Marrow Sampling Times Used in 50 R and 100 R TBI Study for All Patients

Radiation Day	-7	-3	0	+1	+2	+3	+4	+7	+14	+21	+28	+35	+42
Bone Marrow		x					x				x		
WBC, RBC, Platelets Blood Film, Hgb., Hct.	x	x	x	x	x		x	x	x	x	x	x	x
Uric Acid		x	x	x			x	x	x	x	x		

Table 4

Range of Pretreatment Blood Values Among Patients in Each Category

(Average of Day -3 and Day 0)

Diagnostic Group	No. of Exposures	Leukocytes mm^3 x 10^3			Absolute Lymphocytes/mm^{3}x 10^3			Platelets/mm^3 x 10^3			Hemoglobin gm/100 ml		
		Range		Geom. Mean	Range		Geom. Mean	Range		Geom. Mean	Range		Geom. Mean
		High	Low		High	Low		High	Low		High	Low	
Polycythemia Vera 100 R	8	41.6	10.0	25.3	4.2	1.2	2.1	1,619	289	806.1	15.9	11.6	13.6
Chronic Lymphocytic Leukemia - 50 R	15	304.0	9.8	83.5	294.9	9.4	76.9	337	40	131.9	16.8	8.3	12.5
Chronic Lymphocytic Leukemia - 100 R	20	396.2	6.2	69.8	388.6	4.3	61.4	412	13	113.1	14.8	6.9	11.4
Chronic Granulocytic Leukemia - 50 R	8	463.9	52.1	114.5	9.8	1.4	3.5	1,061	211	446.5	14.2	9.0	11.3
Chronic Granulocytic Leukemia - 100 R	4	246.3	103.8	148.5	4.2	0.9	2.1	1,326	392	707.5	12.0	9.0	10.4
Malignant Lymphoma 50 R	5	14.2	6.5	9.6	9.9	1.6	4.5	238	50	134.1	16.2	9.7	13.5
Malignant Lymphoma 100 R	22	28.3	2.3	7.7	26.9	1.1	3.4	444	45	205.0	15.8	8.5	12.4
Hodgkins - 50 R	1			10.0			2.9			310			11.0
Hodgkins - 100 R	2	11.5	9.0		10.3	2.0		521.2	481.2		10.2	8.2	

Bone-marrow aspirations were performed according to the protocol described; we have decided not to present the findings in the present report.

Laboratory Methods

The hematologic studies were performed on venous blood samples using well established laboratory methods. The hemoglobin value was determined by the cyanmethemoglobin method and hematocrit percent by the Wintrobe method. Leukocytes and erythrocytes were counted electronically. Platelets were enumerated by the method of Brecher and Cronkite using phase microscopy (13). When platelet counts were low, dilutions of 1:20 were used rather than 1:100. The number of small squares counted in the chamber was increased to 10, 25, or 50 until more than 100 platelets were counted, or all platelets in 50 squares counted. In determining absolute lymphocyte values for patients with PRV, we performed differential counts on 400 leukocytes for greater statistical confidence.

The Radiation Facility and Dosimetry

The irradiation room, designated the medium-exposure-rate total-body irradiator (METBI), was completed in 1959; it is an eight-foot cube, concrete shielded, with a 385-curie source of cesium-137 in each of the eight corners. A maze connects the treatment room to its control room where a nurse or operator is in visual contact with the patient by a series of mirrors. The patient lies on an aluminum bed suspended in the center of a homogenous 2 x 2 x 6 foot radiation field. The beams from the eight sources are shaped so that the exposure rate is uniform to within ± 5% within the treatment volume. The exposure rate can be varied by a series of attenuating filters and values from 0.64 to 1.52 R/min have been used; but most treatments were given at 1.50 R/min. This facility has been described in detail by Brucer (14) and a detailed description of the radiation field has been published (15).

We made two independent dosimetry studies to determine the dose received by patients. We filled three compartmentalized phantoms with Fricke chemical dosimeter and determined spectrophotometrically the average dose to each of the 13 compartments. In addition, we measured the midplane isodose lines by an ionization probe; details are given by Hayes et al (16). In the second study,* with a tissue-equivalent plastic phantom containing an implanted skeleton and density-adjusted lung spaces, we measured the dose to various organs using LiF thermoluminescent dosimeters in the volumes representative of these organs. Except for the bone marrow, the average rad response of the dosimeters in an organ was defined as the average organ dose. We calculated the marrow dose as a weighted average since this tissue, located at variable depths beneath the

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* W. L. Beck and T. R. Stokes performed the thermoluminescent dosimetric measurements as part of our continuing total-body irradiation program.

Table 5

Variations in Average Dose to Body Compartments According to Body Size

Compartment	Average Compartment Dose in Rads Per 100 R		
	Adult*	Adolescent*	Child*
Head	78	81	79
Neck	76	83	84
Chest	63	66	70
Abdomen	66	69	71
Pelvis	65	70	71
Arms	76	78	75
Thighs	75	78	82
Legs	86	88	87
Feet	76	78	81
Whole Body	70	74	75

*Hayes Water Phantoms

surface, is not placed uniformly in a single, well defined site. The assumed marrow distribution used for the dose estimates was that suggested by R. E. Ellis (17) for a normal man. It is well known that its volume and location varies widely in patients with the diseases studied here.

The average tissue dose to the total torso of a standardized normal adult was estimated by each of the dosimetry studies to be 65 rads/100-R exposure by the compartmentalized phantom study and 68 rads/100 R by the heterogeneous phantom. The minimal bone-marrow dose occurs in the pelvic region and is only 53 rads/100 R. Variations in dose due to difference in body size and configuration are shown in Table 5. Table 6 lists the absorbed dose in various organs.

OBSERVATIONS

Chronic Lymphocytic Leukemia

During the first six weeks after therapy in 35 patient treatments with either 50 R or 100 R, palpable lymph nodes shrank in 20 and remained unchanged in 12.

Table 6

Anatomical Organ Doses in Cesium-137 Total-Body Irradiation Facility

Organ	Total Organ Dose (Rads/100 R)		
	Average	Ranges	
Bone Marrow	64	53-86	(137)*
Cerebellum	77	74-81	(9)
Cerebrum	75	70-79	(21)
Heart	66	58-70	(16)
Intestines	67	54-76	(107)
Kidneys	66	62-70	(6)
Lenses of Eyes	87	85-90	(2)
Liver	67	61-78	(42)
Lungs	67	58-77	(185)
Skin (above sternum)	73	72-75	(2)
Skin (front waist)	74	72-75	(2)
Spleen	69	64-73	(7)
Stomach	64	59-69	(34)
Thyroid	76	75-77	(2)

*Figures in parentheses indicate the number of bodily locations where dose was measured with LiF dosimeters.

Of the palpable spleens, ten were smaller after treatment, seven remained unchanged, but palpable, and seven enlarged during the same interval. There was no clear pattern of change in liver size.

Twelve patients gained weight, 13 lost, and eight had no change. (The others are unrecorded.) The general feeling of well-being improved to some degree in 21, remained unchanged in 12, and decreased in two. We could not demonstrate with any of these clinical responses that the effect of 100 R was greater than that of 50 R, although the small numbers of patients is a deterrent to comparisons.

Figure 1 shows the WBC responses of individual patients to 50 R and Fig. 2 those to 100 R. Radiosensitivity differed considerably from patient to patient. In both groups of patients (50- and 100-R exposures) there was a subgroup of "resistant" patients whose response was significantly less pronounced. There was no trend of climbing toward pretreatment values by day 42 in either dose or sensitivity subgroup.

Figure 3 shows the changes in mean blood lymphocyte numbers following 50-R and 100-R exposures in the resistant and sensitive patients. We saw no statistically significant differences in the degree of lymphocyte depression caused by these two doses. Although the most rapid fall occurred in the first week, a nadir was not reached until three or four weeks after exposure.

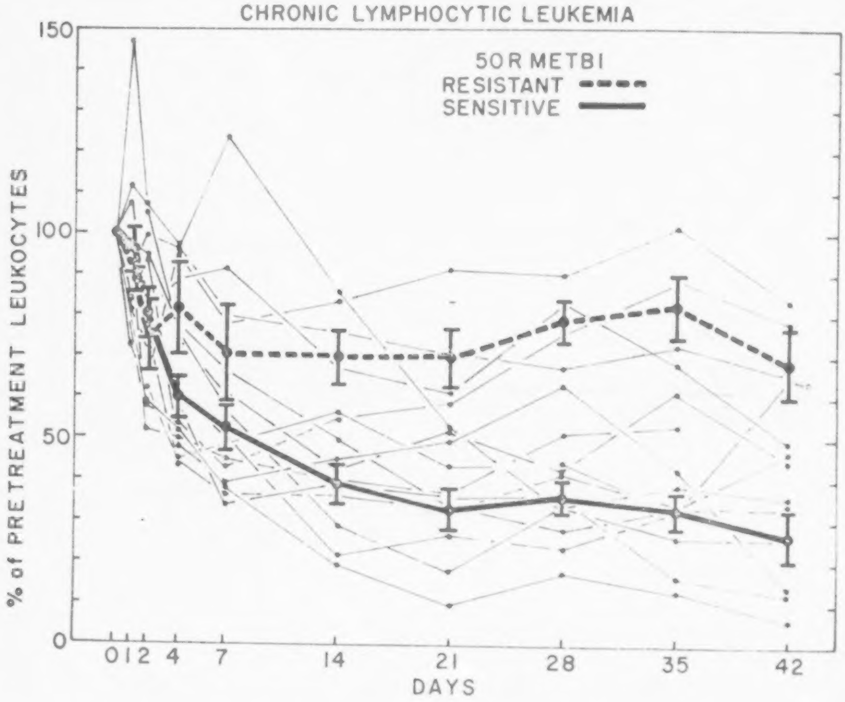

Fig. 1. Changes in the white blood levels in 15 patients with chronic lymphocytic leukemia after 50 R. The leukocyte counts have been normalized to the individual patient's pretreatment values. Two geometric means with their standard errors are shown; one (solid line) is that for the leukocyte levels in the 11 more responsive patients and the other (dotted line) is that for the four patients whose course seems more resistant. The two computed means (after seven days) are statistically different at the 95% confidence level.

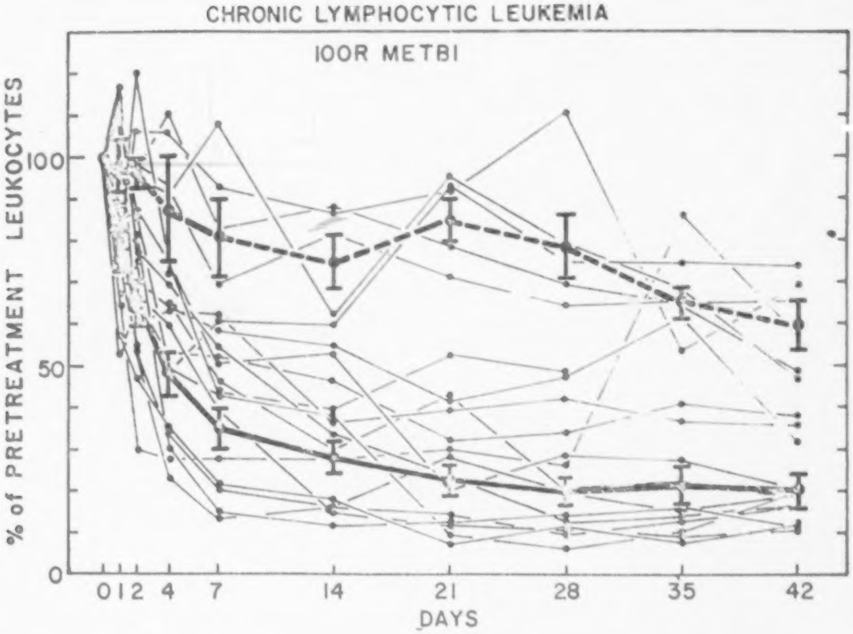

Fig. 2. Changes in the white blood counts (shown in Fig. 1) of 19 patients with chronic lymphocytic leukemia after 100 R. As in Fig. 1, the two geometric means are those for the 14 "sensitive" and five "resistant" patients and are significantly different at the 95% level from the second day onward.

The response of leukemic lymphocytes to 100 R was unrelated to the level of the pretreatment leukocyte counts, nor did it correlate with lymphocyte size, notching of nuclei, or tendency to smudge. The degree of marrow infiltration as judged by histologic examination of marrow aspirated did not tell us why some patients had "radioresistant" lymphocytes. Furthermore, we found no correlation between the lymphocyte response and the clinical response or length of "remission"; eight patients required no other treatment for seven and a half or more months, while nine patients needed additional treatment for leukemia shortly after the study period, less than three months from the irradiation.

While the leukemic lymphocytes responded similarly to 50 R and 100 R, the effect of these two doses on the platelet levels differed strikingly as shown in Figs. 4 and 5. These graphs show also that the responses of patients given 50 R vary more than those of patients given 100 R, suggesting that recovery may be manifested more variably with the lower dose. A trend toward recovery is definitely established during the fifth and sixth weeks after exposure. As can be seen in Fig. 6, the recovery in numbers of circulating platelets after 50 R occurs earlier and more rapidly on the average than after 100 R. The standard errors of these geometric means are also larger with the lower dose indicating the greater variability of the response to the lower dose.

Hemoglobin values remained stable in the 10 patients not anemic before treatment; those that were anemic usually had no rise in their hemoglobin levels or became more anemic during the six weeks following irradiation. In a few patients who had been requiring transfusions before treatment, the 100-R exposure increased the number of transfusions needed while 50 R did not (see Table 2).

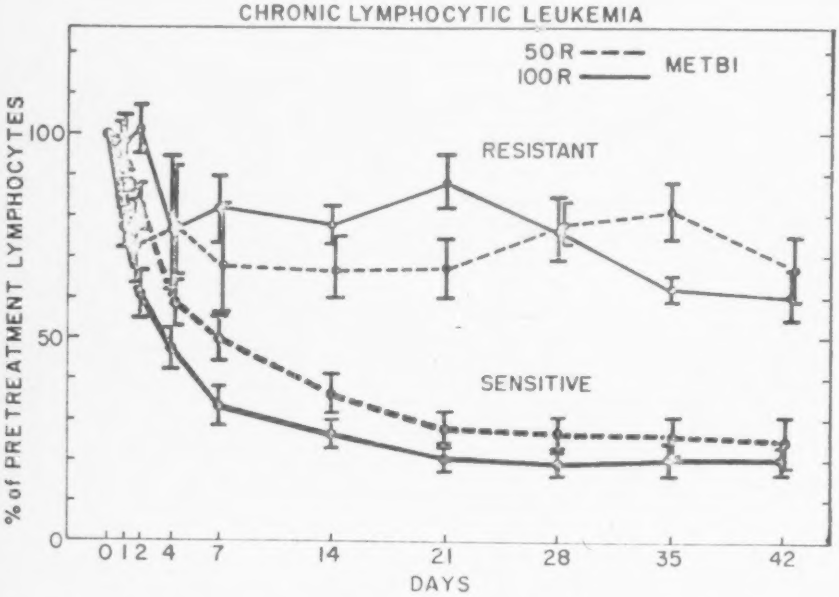

Fig. 3. Changes in the geometric-mean blood lymphocyte values (shown as normalized percentages of pretreatment differential lymphocyte counts) for the patients with chronic lymphocytic leukemia whose changes in white blood cell values are shown in Figs. 1 and 2. There is no statistical difference between the computed mean changes after 50-R and 100-R exposures in either the "sensitive" or "resistant" groups but the statistically valid difference between the mean responses of the two groups is obvious.

Malignant Lymphoma

This group of 20 patients included five who were given 50 R, two of whom subsequently received 100-R treatments. Of the 17 patients who received 100 R,

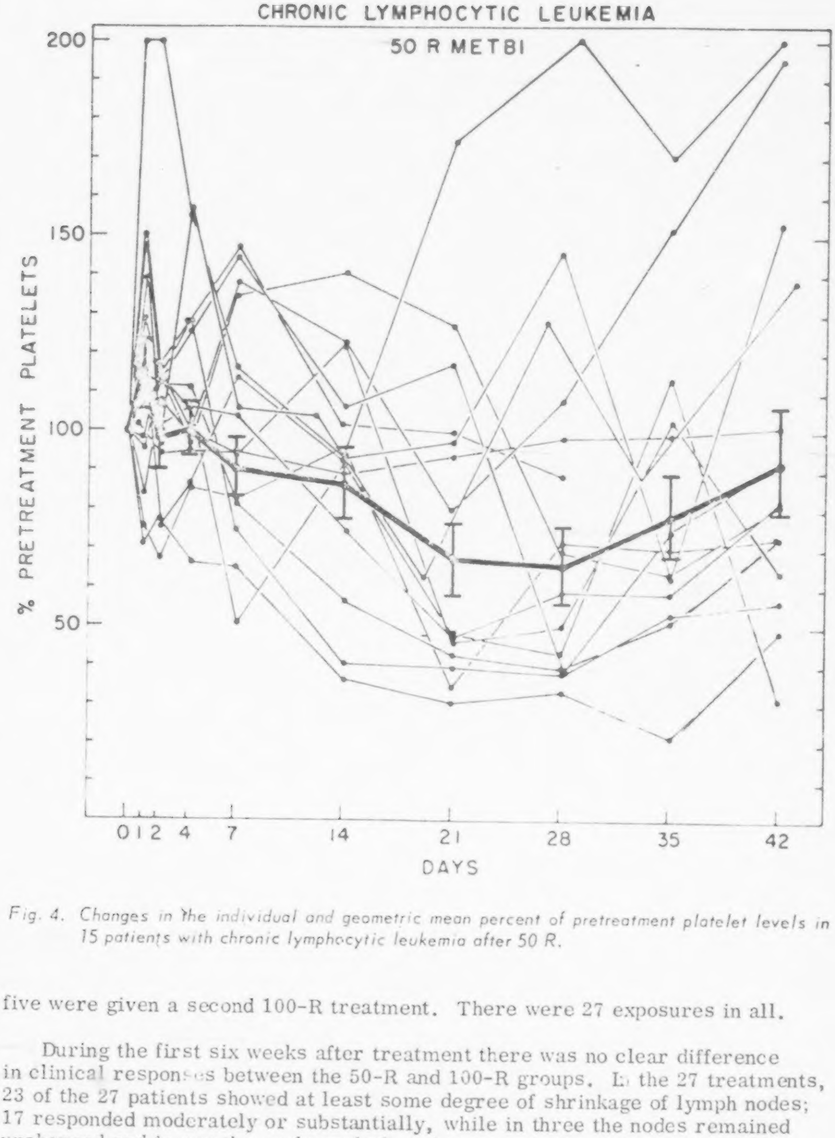

Fig. 4. Changes in the individual and geometric mean percent of pretreatment platelet levels in 15 patients with chronic lymphocytic leukemia after 50 R.

five were given a second 100-R treatment. There were 27 exposures in all.

During the first six weeks after treatment there was no clear difference in clinical responses between the 50-R and 100-R groups. In the 27 treatments, 23 of the 27 patients showed at least some degree of shrinkage of lymph nodes; 17 responded moderately or substantially, while in three the nodes remained unchanged and in one they enlarged after therapy. In the eight patients with palpable spleens, only two spleens definitely regressed, while five others remained large and one was questionably changed. Nine palpable livers regressed while eight remained unchanged or enlarged. There was no consistent pattern of change in body weight. The subjective general feeling of well-being remained poor or unchanged in 17 patients, while 10 expressed some degree of improvement.

Most of these patients had at least a few atypical lymphocytes in the blood, and we were unable to separate definitely those that should be considered as having a "leukemic" stage of lymphosarcoma, except for two who had larger numbers of abnormal cells. These two patients described in a later paragraph responded

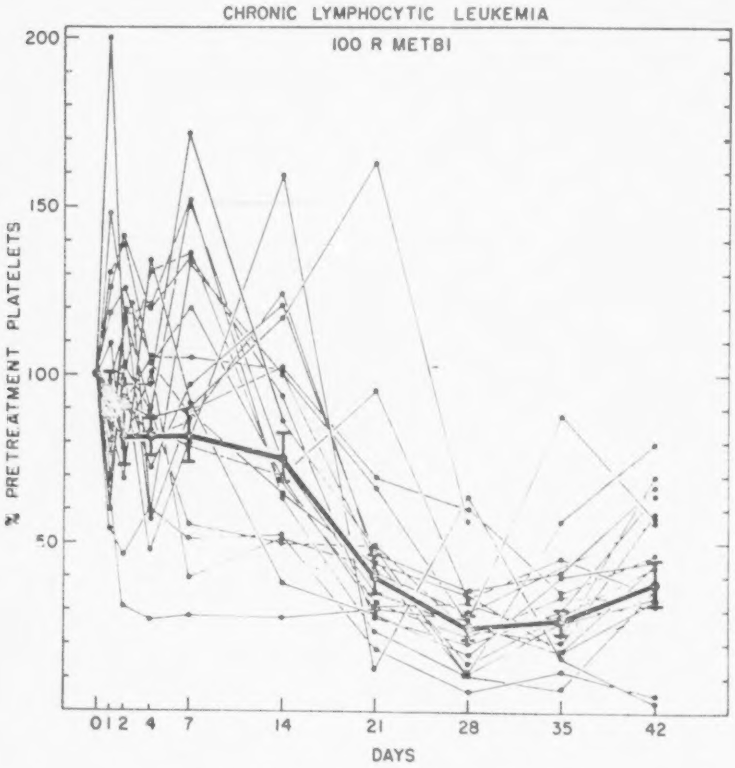

Fig. 5. Changes in the individual and geometric mean percent of pretreatment platelet levels in 20 patients with chronic lymphocytic leukemia after 100 R. Comparison of the geometric means and their standard errors in this figure and in Fig. 4 shows that the degree of response in the two dosage groups differs significantly from 21 days on. Five individual patients who received 50 R, however, reacted as the 100-R group, while three in the 100-R group responded similarly to the 50-R patients.

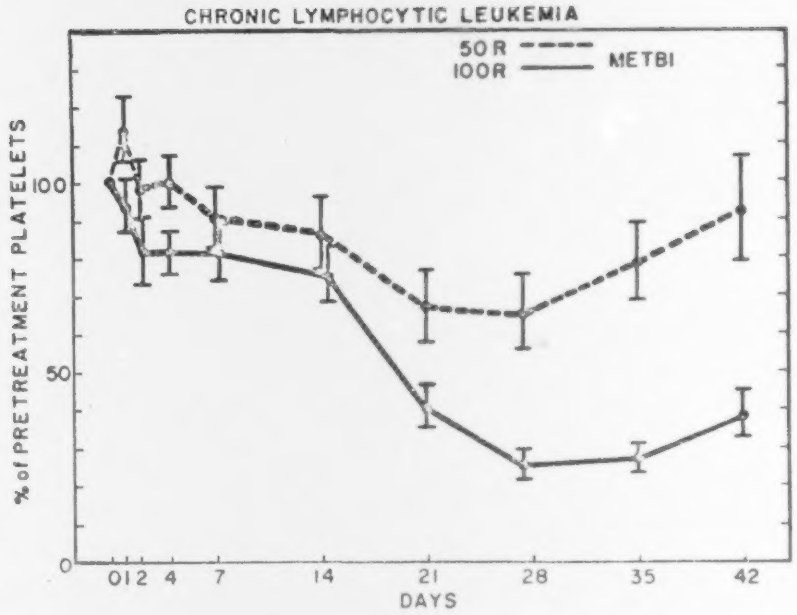

Fig. 6. Comparison of the geometric means for blood platelet levels in patients with chronic lymphocytic leukemia after 50 and 100 R. The curves become statistically different only after 21 days.

quite differently from the rest of the group. All the others had pretreatment leukocyte counts of less than 15,000/mm^3; the numbers of lymphoid cells were less than 11,000/mm^3. The subsequent decrease in lymphocytes was not great (the lowest value was about 50% of pretreatment level, reached at seven days). In the majority of the patients (11/17) lymphocyte levels began to recover from this decrease by 14 days; this was unlike the response in CLL. In Fig. 7 the geometric means for the leukocytes of the main groups of patients with malignant lymphoma who received 100 R are plotted, along with one standard error of the mean. The changes in total leukocytes after 100 R in patients with malignant lymphoma have been graphed in Fig. 7 for comparison with later graphs in this study and with those of other investigators who have not differentiated the hematologic response of the various white blood cell types. In Fig. 8 the sequential changes in lymphocyte counts in individual patients can be seen varying widely.

By contrast, in the two "leukemic" patients with high numbers of abnormal lymphoid cells in the blood before irradiation (16,000 and 26,000/mm^3) these cells decreased profoundly and rapidly after 100 R. Their course differed

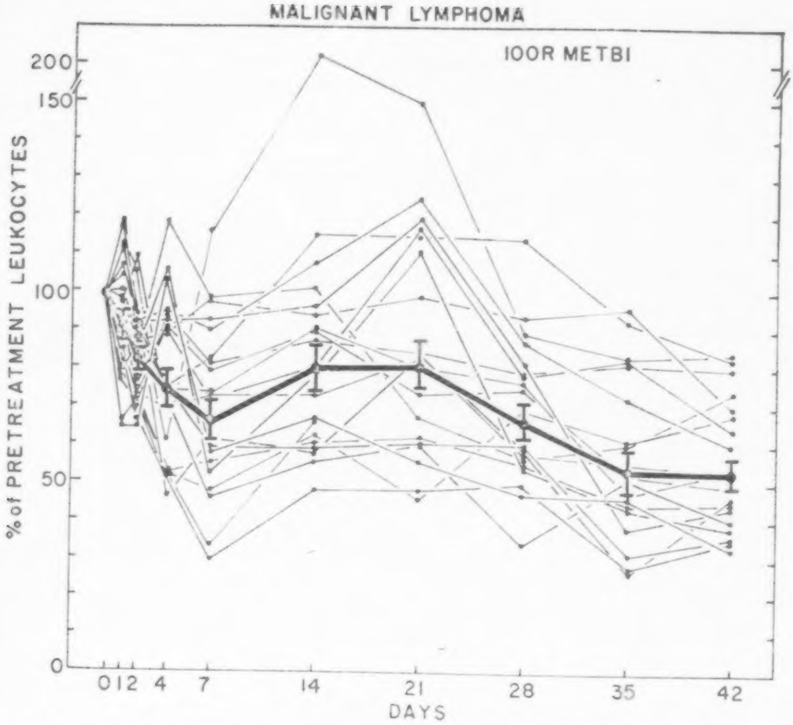

Fig. 7. Changes in blood leukocyte values in 20 patients with malignant lymphoma after 100 R. The actual WBC counts have been normalized to individual pretreatment levels and the geometric mean and its standard error computed on this basis.

considerably from that of the other members of the lymphoma group and resembled more closely the extreme responders of the chronic lymphocytic leukemia groups. (See Figs. 1-3).

The platelet values for the 50-R group dropped only slightly on the average and varied widely from patient to patient. In the 100-R group, the platelets responded more consistently; a steep drop appeared during the third and fourth weeks and reached a nadir of 27% of the pretreatment values. This curve resembles quite closely that of the patients with chronic lymphocytic leukemia given the same dose (Fig. 4). All showed a trend toward recovery during the fifth and sixth weeks (Figs. 4 and 10). Hemoglobin values did not change significantly during the six weeks after irradiation with either 50 R or 100 R.

Hodgkin's Disease

Only three patients with Hodgkin's disease were treated. One patient who received 50 R early in her disease failed to respond and was quickly transferred to more conventional therapeutic regimens. The second patient, who received 100 R, showed similarly no benefit, and the third one failed to return after two weeks for further follow-up studies. The platelet and lymphocyte responses for the 50-R and 100-R exposure behaved as in patients with other types of lymphomas.

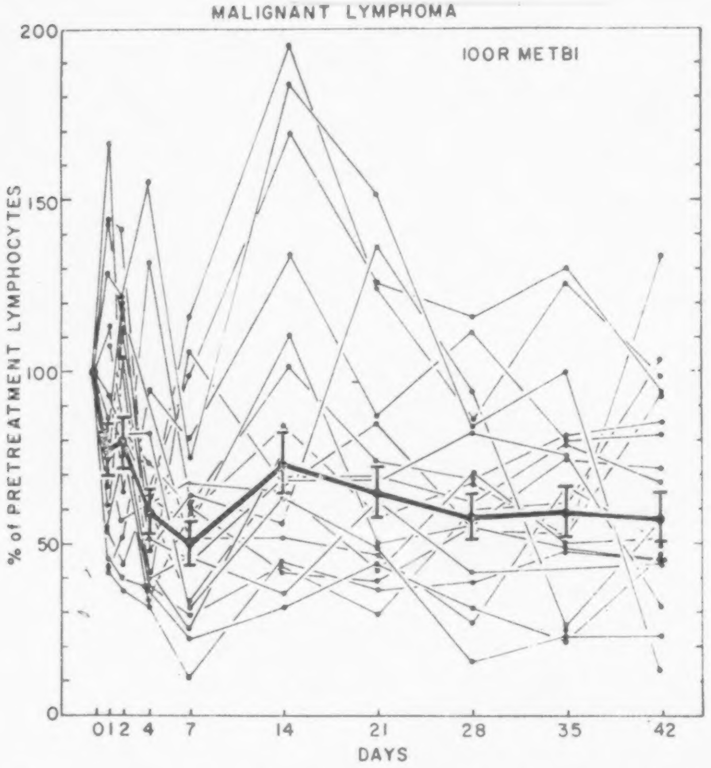

Fig. 8. The changes in Fig. 7 are shown here as changes in lymphocyte levels computed from individual absolute lymphocyte counts before and after exposure. These extremely variable responses of individual patients reduce to a geometric mean not statistically different from that of the "resistant" type of response in lymphocyte levels of patients with chronic lymphocytic leukemia treated with either 50 or 100 R (see Fig. 3). In several of these patients total-body irradiation obviously resulted in lymphocytosis in relation to pretreatment levels.

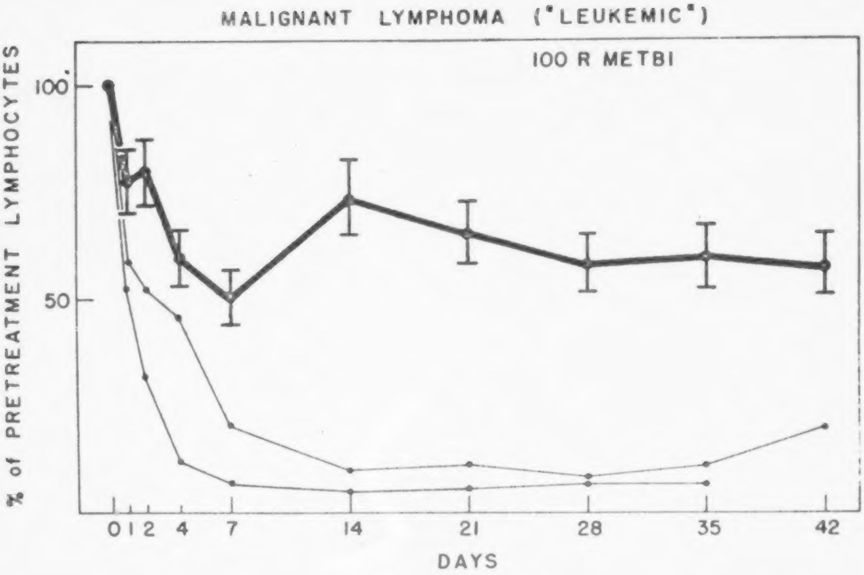

Fig. 9. The lymphocyte response curves of two patients with "leukemic" malignant lymphoma were so atypical in comparison with those of the 20 other patients with this disease (Fig. 7) that they are shown here separately along with the geometric mean of the other 20 patients. These two individual lymphocyte response curves fit within the 95% confidence limits of the "sensitive" type of lymphocyte response curves shown for chronic lymphocytic leukemia in Fig. 3.

Chronic Granulocytic Leukemia

This group included eight patients exposed to 50 R and four exposed to 100 R. Their spleens remained palpable and unchanged in size in eight, became slightly smaller in one, and distinctly smaller in one. In the other two, the spleen was not palpable before or after treatment. A definite decrease in liver size was recorded in only one patient. The general feeling of well-being was improved in eight patients but unchanged in three and poorer in one.

All patients had high initial leukocyte counts consisting predominantly of mature granulocytes. Nongranulocytic elements were so few that the curves shown in Figs. 11 and 12 can be considered as representing chiefly changes in granulocytic numbers. The numbers of leukocytes began a decrease promptly after these doses and the degree of fall indicated a greater radiation sensitivity than we see in normal granulocytes (see Fig. 7). Further, this depression usually persisted longer than would a similar degree of depression produced in normal persons by a higher dose as in radiation accidents. After 50 R the decline in values began promptly, the mean dropping to 55% on day seven, 48% by day 14, then staying in this range for the six-week period of observation (Fig. 11). The response of the four patients given 100 R (see Fig. 12) was similar to that of the 50-R group, but the degree of depression was greater: 35% on day 7, 21% on day 14. By day 21, three of the four patients had granulocyte levels below 20% of pretreatment levels; one patient showed a transient partial recovery pattern. This suppression persisted throughout the 42-day period at the end of which there was still a trend toward even lower levels.

The platelets in CGL before treatment were either in the normal range or elevated; in a few instances they were at levels over 1,000,000/mm^3. After 50-R exposures, the platelet counts rose to a mean level of 136% by day 14 before declining to a nadir of 82% on day 28. The means then returned toward the pre-

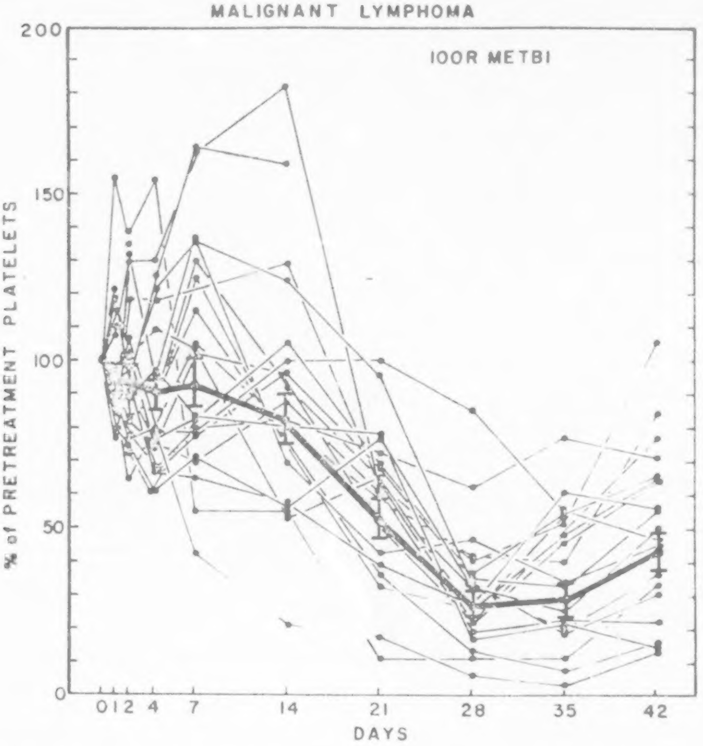

Fig. 10. Platelet response curves in patients with malignant lymphoma exposed to 100 R. The heavy solid line represents the geometric means and their standard errors. The curve closely resembles that in Fig. 6 of chronic lymphocytic leukemia after 100 R.

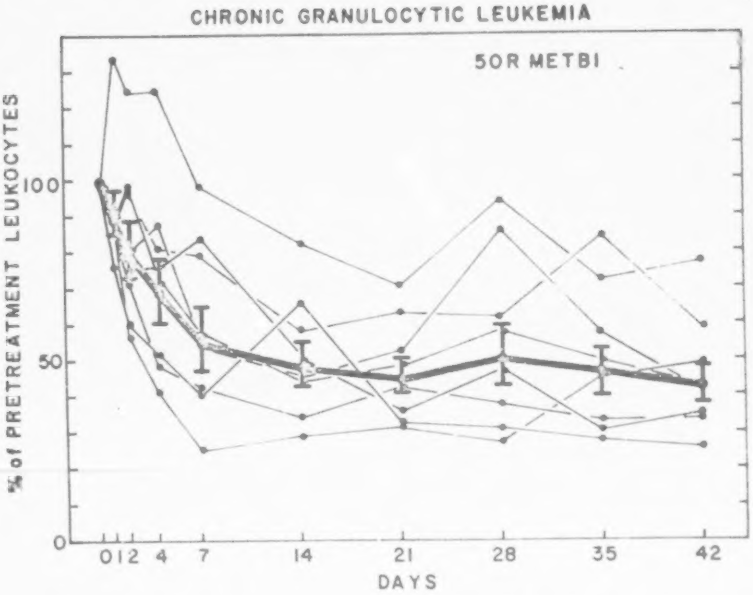

Fig. 11. Changes in blood leukocyte values, expressed in terms of individual pretreatment WBC counts, of eight patients with chronic granulocytic leukemia exposed to 50 R. The dark solid line represents the geometric means and their standard errors.

treatment range during the fifth and six weeks (Fig. 13), but the values ranged widely (53% to 191% of pretreatment values).

The platelets of the group exposed to 100 R also rose during the first two weeks but much less conspicuously (Fig. 14). The subsequent depression followed the usual temporal pattern and reached a nadir of 48% on day 42. This progressive decrease which persisted beyond 42 days is presently being observed also in our ongoing studies with fractionated and low-dose-rate exposures. A comparison of mean responses for platelets and leukocytes after 50 R and 100 R is made in Fig. 15.

The percent response (relative to pretreatment values) of the leukemic granulocyte appears from this graph (Fig. 15) to be about a factor of two greater than that of the platelets. The comparison here shows that in the occasional patients where injury to the platelet system is to be avoided because of borderline thrombocytopenia, a 50-R exposure would offer some therapeutic effect on granulocyte numbers while sparing platelet numbers.

Mean hemoglobin values were not significantly altered during this period of study. Figure 16 shows the hemoglobin values for the patients who received 100 R.

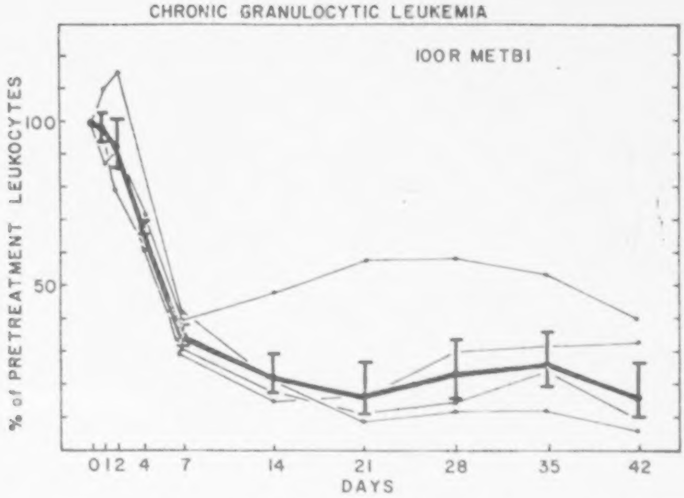

Fig. 12. Changes in blood leukocyte values, expressed in terms of individual pretreatment WBC counts, of four patients with chronic granulocytic leukemia exposed to 100 R. The dark solid line represents the geometric means and their standard errors.

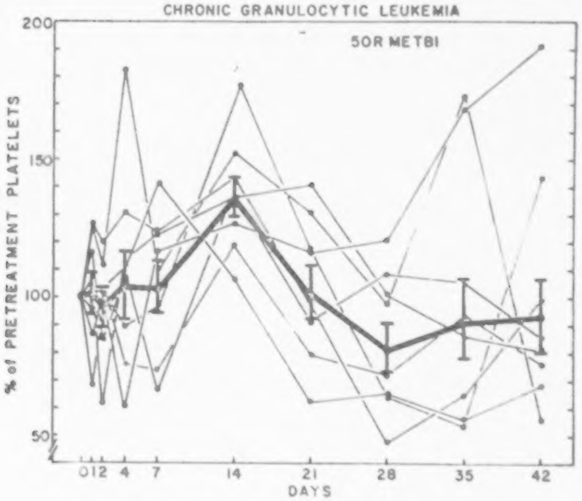

Fig. 13. Changes in platelet values expressed in terms of individual pretreatment platelet counts of eight patients with chronic granulocytic leukemia exposed to 50 R. The dark solid line represents the geometric means and their standard errors.

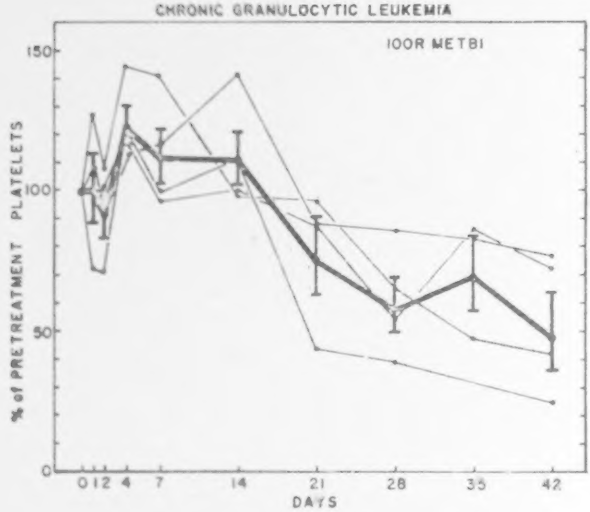

Fig. 14. Changes in platelet values, expressed in terms of individual pretreatment platelet counts, of four patients with chronic granulocytic leukemia exposed to 100 R. The dark solid line represents the geometric means and their standard errors.

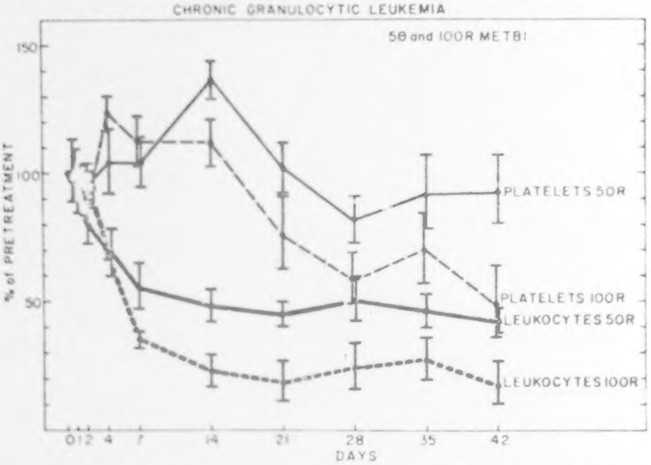

Fig. 15. Comparison of the geometric means of the leukocyte and platelet values in chronic granulocytic leukemia exposed to 50 and 100 R, shown in Figs. 13 and 14, showing the greater sensitivity of the leukocytes of these patients. In comparison with the curves for platelets (Fig. 6) in chronic lymphocytic leukemia, changes after 50 and 100 R occur earlier and are more extreme.

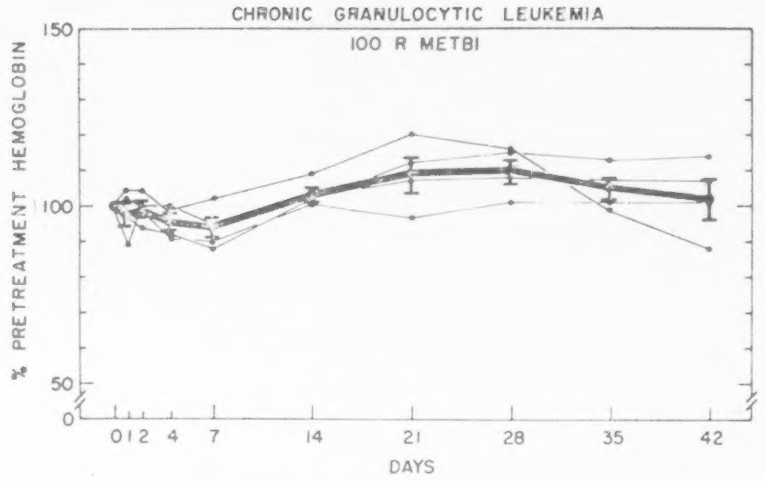

Fig. 16. Changes in blood hemoglobin values in four patients with chronic granulocytic leukemia exposed to 100 R showing a slight improvement relative to initial hemoglobin levels.

Polycythemia Rubra Vera and Primary Thrombocythemia

This group included eight patient-exposures to 100 R. Six patients had polycythemia rubra vera (PRV); one received two separate treatments (seven treatments); the seventh patient had primary thrombocythemia. In five patients there was an improvement in general feeling of well-being; in three there was no change. Of the large spleens, the size decreased in three, increased in one, and remained unchanged in two. The effects on liver size were slight and variable. In six patients a significant gain in weight was recorded.

All the PRV patients had initial leukocyte counts above 10,000/mm^3. These ranged up to 41,000/mm^3 pretreatment. As is shown in Fig. 17, leukocyte values began to drop after one week and reached their nadir at the six-week point, considerably later than has been observed in normals or in patients with most other diseases. As with platelet values (see below), the return of the leukocyte level toward normal was slow and was prolonged up to six months. The changes in absolute lymphocyte values in relation to pretreatment levels after 100 R (Fig. 18) were more like those after 100-R accident cases. Typically no return to normal was seen during the 42-day observation period.

Except for one patient with a normal platelet count, all had pronounced elevated platelet counts ranging from 575,000 to 1,600,000/mm^3 before treatment. The qualitative platelet responses to 100 R were similar to those of accidentally irradiated normal persons and of patients without leukemic diseases in that a nadir was reached at about 30 days (Fig. 19), but characteristically the fall in

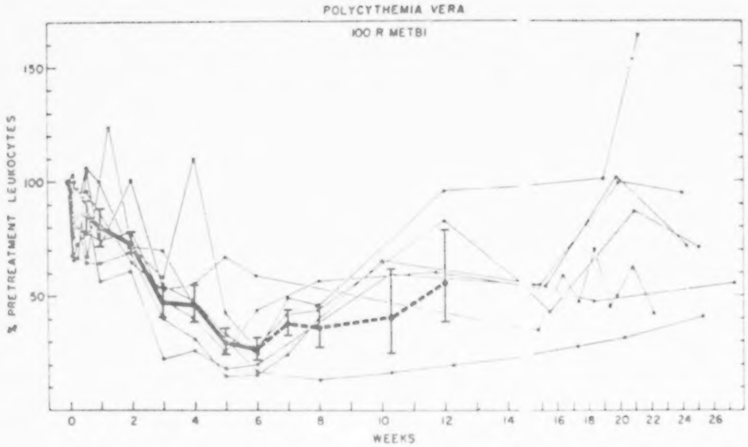

Fig. 17. Changes in blood leukocyte levels in eight patients with polycythemia rubra vera after 100 R. The solid heavy line is the geometric mean of these values through the usual 42-day postirradiation study period; the dotted line extends this mean through less regularly obtained data points over six months.

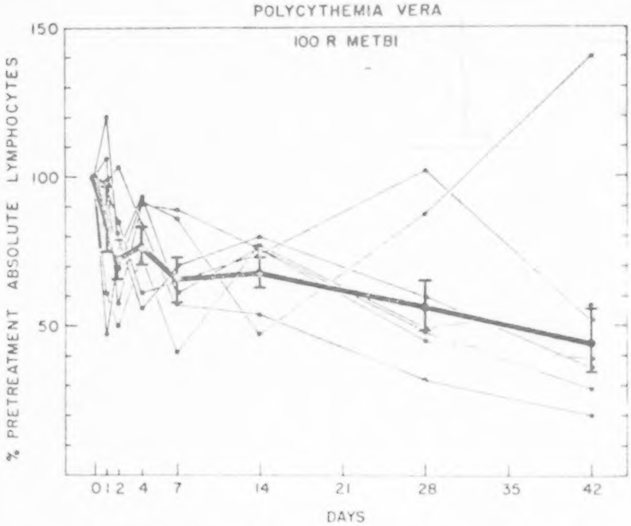

Fig. 18. Changes in blood lymphocyte values in seven patients with polycythemia rubra vera exposed to 100-R total-body irradiation. To improve statistics, 400 leukocytes were counted at each data point. One patient whose baseline values were believed to be unreliable is excluded from this figure.

count either did not begin for two weeks or was slight until that time. The return toward normal, however, was much delayed and did not reach pretreatment levels for many months. This temporal pattern differs distinctly from the response of accident victims where a return to normal (or even a rebound elevation) occurs within six weeks. It appears that some homeostatic mechanism tends to prevent platelet values from returning to abnormal pretreatment values. Figure 19 shows the platelet response during the usual six-week study period and for the following six months.

Hemoglobin values for this group were not significantly elevated at the time of treatment; excessively high platelet and leukocyte values dominated their blood picture. Evaluation of changes in red cell numbers and morphology was complicated by pretreatment phlebotomies, stage of disease, and previous marrow-depressing treatments with ^{32}P or drugs (only two of the six were new, untreated cases). Hemoglobin and hematocrit values changed little after treatment (Figs. 20, 21) with 100 R. We believe, however, that this dose suppressed the rise that usually would have occurred with therapy. The mean corpuscular hemoglobin concentration before treatment was invariably low, due to phlebotomies and intestinal bleeding. It did not change in the postirradiation period (Fig. 22).

There was a 12% decrease in numbers of RBC and 12% increase in mean corpuscular volume that offset one another so that little or no change was seen in hematocrit values. Blood volume studies, however, were not done. Generally the mean corpuscular hemoglobin concentration did not change significantly

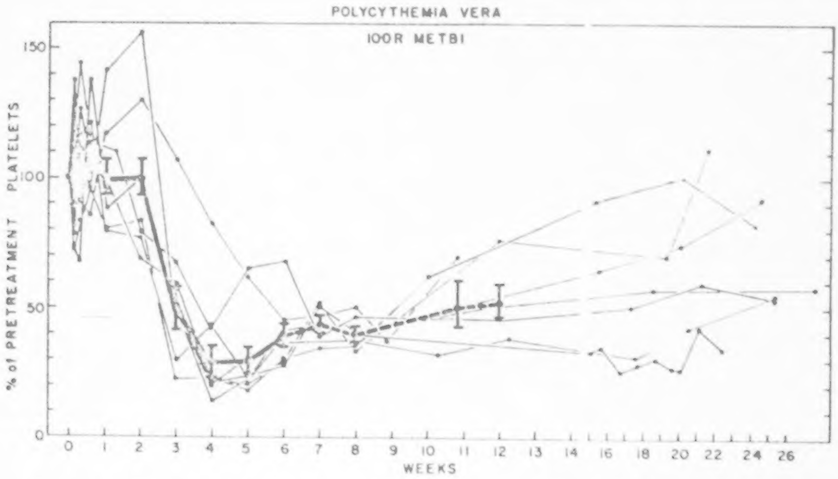

Fig. 19. Changes in blood platelet levels in eight patients with polycythemia rubra vera exposed to 100 R. Geometric mean is shown on a solid heavy line for 42 days of the protocol and as a broken line after that time when data points were less rigidly obtained.

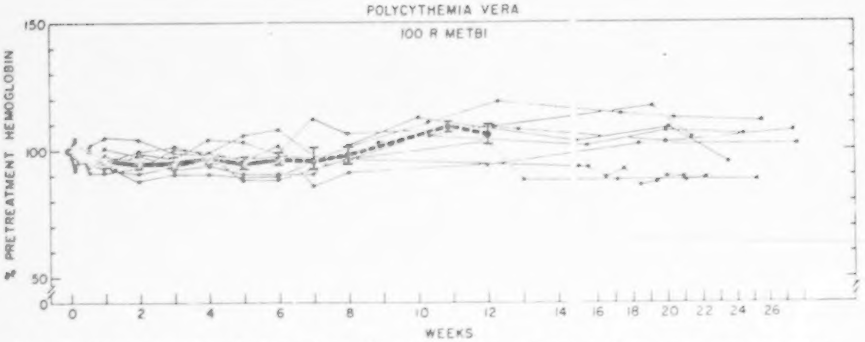

Fig. 20. Changes in hemoglobin values of eight patients with polycythemia rubra vera over the six months after 100-R exposure.

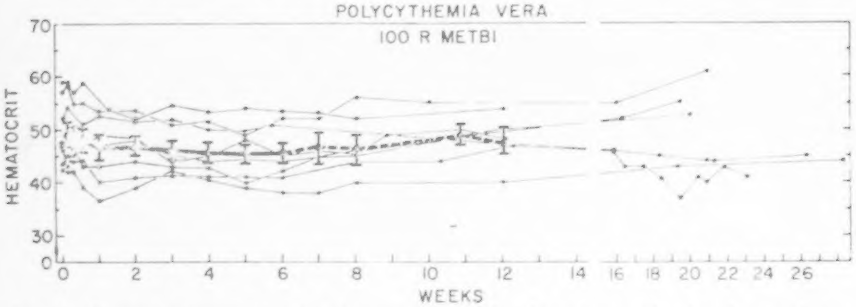

Fig. 21. Changes in hematocrit values (not normalized) of eight patients with polycythemia rubra vera over the six months after 100-R exposure.

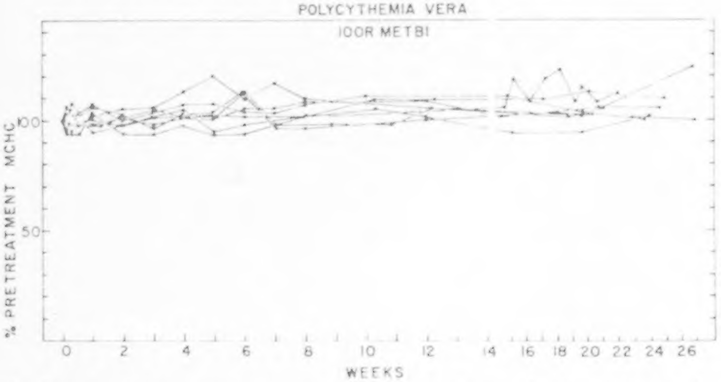

Fig. 22. Changes in mean corpuscular hemoglobin concentration of eight patients with polycythemia rubra vera over the six months after 100-R exposure.

but in some individuals it rose 10 to 20% (Figs. 22 and 23).* Detailed red cell values in one patient are shown for a 26-week period (Fig. 23). The principal clinical problem in this patient was her excessively high platelet count which ranged above 1,000,000/mm^3 and was believed to be a factor in intestinal hemorrhage and its associated iron loss.

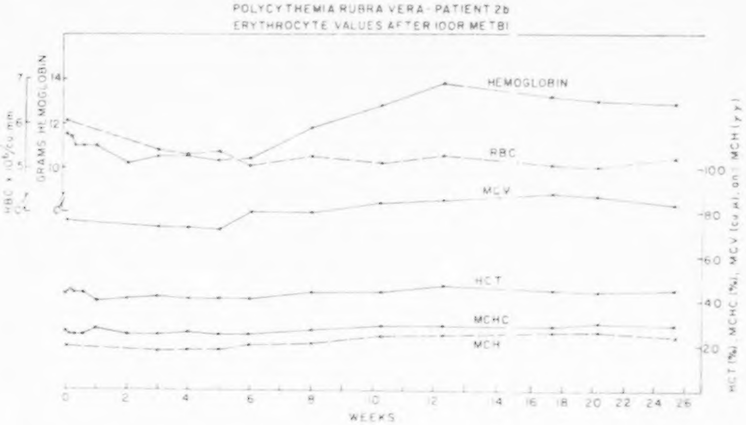

Fig. 23. Changes in actual values of blood erythrocyte parameters in one patient with polycythemia rubra vera treated with an exposure of 100 R.

Changes in Uric Acid

In all disease categories and both dose groups, we examined serum uric acid levels. After exposure, the levels changed, as might be expected from previous observations, but in this series of patients the changes were, in general, small, inconsistent, and of little clinical value. In some patients an early increase and subsequent decrease were sufficiently large to be accepted as indicative of the tissue destruction caused by the radiation exposure.

In 100-R treated lymphosarcoma and CLL, there were increased average levels on postirradiation days through four or seven (Table 7). Among the patients given 50-R exposure the CGL group showed elevated uric acids on only the second day

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* In a study of RBC size distribution after low-dose-rate total-body irradiation (to be reported elsewhere; see ORAU Medical Division Research Reports 1968, 1969), we have found by electronic measurements of red cell size that irradiation produces changes in cell volume that are not demonstrated by measurements of hemoglobin, hematocrit, and cell numbers/cm^3. We are finding that the erythron returns to normal within 120 days in this study only if iron stores have not been depleted by phlebotomy or hemorrhage.

Table 7

STATISTICAL SIGNIFICANCE OF OBSERVED MEAN SERUM URIC ACID LEVELS AFTER TBI

Disease Category	TBI (R)	Days 1	2	4	7	14	21	28
Lymphosarcoma	50	0 (5)*	0 (5)	0 (4)	0 (5)	0 (5)	0 (4)	0 (4
	100	0 (15)	+ + (16)	+ + (17)	0 (17)	0 (17)	0 (15)	0 (11)
Polycythemia	100	0 (7)	0 (5)	0 (7)	0 (7)	0 (7)	0 (7)	- (6)
Chronic Granulocytic Leukemia	50	0 (7)	+ (7)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)
	100	0 (3)	0 (2)	0 (3)	0 (4)	0 (4)	0 (2)	- (3)
Chronic Lymphocytic Leukemia	50	0 (15)	0 (14)	0 (14)	+ (15)	0 (15)	0 (14)	0 (13)
	100	0 (14)	+ + (15)	+ + (15)	+ (14)	0 (15)	0 (15)	0 (13)
All Disease	50 or 100	0 (66)	+ + (61)	+ + (68)	0 (69)	0 (69)	0 (64)	- (57)
Uric Acid $\overline{X}$	pre-treatment 5.82	6.18	6.48	6.38	6.04	5.67	5.68	5.38
mg/100 ml ± S.D.	1.75	1.73	1.82	2.02	1.99	1.75	1.60	1.71

*Figures in parentheses indicate the number of patients in each group.

0 = No statistically significant change from pretreatment levels.

+ = Increase $P \leq 0.05 - 0.01$; + + $P \leq 0.001$

- = Decrease $P \leq 0.05 - 0.01$

and the CLL group on only the seventh day. In other disease categories and exposure groups no statistically significant early changes were found in the mean values from day to day, although some individual patients, even in these groups, showed alterations that possibly reflected increased cellular destruction. On day 28 following 100 R a decrease was seen in some disease categories and in the averaged data for all, but was not found in individual groups after 50 R.

These observations are compatible with the view that change in uric acid level is a dose-related response that is modified by at least three factors: the amount of radiosensitive tissue present at exposure, the degree of radiosensitivity, and the rate of uric acid production in relation to renal excretory capacity. Appraisal of radiation-induced perturbations in this metabolic system might be better elucidated from study of total urinary uric acid and other protein-related excretory products rather than serum levels.

DISCUSSION

This large amount of hematologic data suffers from the usual variabilities of most clinical investigations — wide range in laboratory values, many of them unexplained, and the lack of a true control population. The information derived, however, is clinically useful and meaningful for radiation biology. The differences in response in different clinical disorders are of special interest and give some insight into the relative dependence of these disease processes on cellular survival and replication. In this discussion "sensitivity" is used to mean simply a response in cell numbers after irradiation; it is not meant to imply any specific mechanism for altered numbers.

Most of the rapid major alterations in blood values during the six-week post-treatment period were the result of irradiation. To be valid, this statement requires us to assume that all peripheral blood cell values would have remained stationary if no treatment had been given. This steady state was not always present. In fact, therapy was often indicated because certain cellular systems were changing, but the rate of change was usually slow in comparison with that induced by irradiation. Patients with chronic leukemia, polycythemia, or lymphoma were in reasonably good condition and the changes in hematologic status that would have occurred in the absence of treatment during the observation period could be predicted with some certainty. For example, most of the patients with chronic leukemia were becoming worse only gradually; white cell levels and symptoms were increasing slowly. Some with lymphocytic leukemia had falling red cell values that required transfusions. Patients with polycythemia were in need of treatment to alleviate symptoms and to lower hazardous elevations in platelet values; two had phlebotomies shortly before irradiation. A rise in red cell values might have been expected had no therapy been given.

Problems of interpreting the quantitative nature of radiation-induced hematologic response have recently been reexamined by Bergner with theoretical and stochastic mathematical models (18). He points out that all curves of blood cell counts are a composite of the effect of radiation damage and its repair, and variations introduced by data that is poor in reliability and numbers. From his theoretical viewpoint he demonstrates that an increase in dose augments the speed of "the response process" as well as the maximum response itself. He feels, however, that large numbers of patients and observations do little for quantitation of the hematologic response and that biologic variation in patients and its many causes force the development of a qualitative rather than a quantitative theory. In attempting this task he shows that the onset of repair processes and their continuance cause the "spread" of the hematologic response data to increase with time. Since larger doses more effectively suppress repair processes and thus tend to reduce one contributing cause to variability, especially later in the course of response, one would expect that larger doses would give more uniform responses. This effect is seen in most of our data but not in all of it. Bergner's analysis of the patients with chronic lymphocytic leukemia, where maximum response of lymphocytes to 50 and 100 R was the same, revealed unexpectedly that greater variability in response (evidence for greater reparative efforts) occurred with the 100-R dose rather than with the 50 R. Since this greater reparative effort after 100 R resulted in a response curve similar to that of 50 R, these observations suggest together that the expected additional cell-damaging response to 100 R was offset by the reparative processes stimulated by the 100 R, thus providing another basis for considering the 100-R dose in this disease unnecessary as well as undesirable. Further analyses, based on Bergner's "Theory of Quantitative Radiation-Response Time-Data," or on other such analytical models, are needed in radiobiology.

When examined from a cytokinetic viewpoint the mechanisms of the changes in blood cell values produced by the irradiation are, of course, complex. This problem has been well discussed by Mathé (19) and Bond et al (20). Presumably radiation-induced death of circulating cells cannot account for much of the total effect of the exposure. Alterations in patterns of tissue sequestration and release of abnormal numbers of cells may have a significant effect upon peripheral blood cell values. The basis for most of the reduction in the cells of the blood, however, is undoubtedly interference with cell proliferation brought about most likely by a radiation-induced decrease in stem cells. Therefore, it may be necessary to relate the patterns of radiation effects to a balance between cell production, release, "normal" life span or turnover rate for each cell type as it occurs in the various disease states, and cellular radiosensitivity. Table 8 lists the geometric means of the minimum blood values reached during the six-week study period in the various diseases studied after the 50-R and 100-R doses.

The patterns of hematologic response to irradiation are influenced by the dose and also by the altered cytokinetic state in each disease. We have attempted, as yet, only preliminary interpretation of our results in the light of these factors.

Lymphocytes

Patients with polycythemia rubra vera provided data on the response of presumably normal lymphocytes to 100 R. An early drop occurred by day two to 76% of pretreatment levels and a gradual decline continued to 53% at the end of the 42-day-study period, so that we do not know the precise time when the lowest lymphocyte values were reached but this curve was most like that of normal men accidentally irradiated.

Table 8

Minimum Geometric Mean Values During 6 Weeks after TBI
Expressed as Percent of Pretreatment Level

	50 R		100 R	
Total WBC				
CLL	34.8	(26.5 good response) (68.3 poor response)	29.7	(19.7 good response) (59.5 poor response)
Malignant Lymphoma	61.8		53.1	
CGL	44.4		17.3	
PRV	-		26.7	
Lymphocytes				
CLL	31.9	(23.7 good response) (66.9 poor response)	26.7	(19.3 good response) (60.6 poor response)
Malignant Lymphoma	59.3		50.0	
CGL	49.4		48.5	
PRV	-		44.4	
Platelets				
CLL	65.0		25.2	
Malignant Lymphoma	70.9		27.3	
CGL	81.5		48.5	
PRV	-		28.6	

Perhaps the most striking observation related to radiation sensitivity of lymphocytes is their response in chronic lymphocytic leukemia to 50 R and 100 R. The two curves are not significantly different. The two series were not entirely comparable and the stage of illness may limit the interpretation of this fact. Our data suggest, however, that if the clinical objectives can be equated with reduction of only the lymphocyte count, the lower dose may be preferable since 50 R appears to reduce lymphocyte numbers adequately with less depression of platelets. Lymphocytes in chronic lymphocytic leukemia are certainly most sensitive to 50 R, and using the lymphocyte response data of the patients with PRV (Fig. 18) as a substitute for our lack of normal control data we can say that those with leukemia are almost three times as sensitive. A comparison with the lymphocyte counts of the Marshallese normals on Rongerik Island (Group III) who were estimated to have been exposed to 78 R (21) also shows that lymphocytes of normal people are less sensitive than those patients with lymphocytic leukemia.

Schrek (22) has reported that some patients with chronic lymphocytic leukemia have radioresistant lymphocytes. In our study (Figs. 1, 2, 3) several of the patients given 50 R or 100 R showed a significantly decreased response, in contrast with the common pattern of a drop to 50% or less of initial values in four or seven days. We have been unable to discern any clear-cut clinical or hematologic correlations with this nonresponsiveness. In some of these patients the resistance of the lymphocytes is actually greater (compare Fig. 3 with Fig. 18) than that of those in PRV (considered to be "normal").

On the other hand, two cases of "leukemic" lymphosarcoma showed inordinately sensitive lymphocytes with an early precipitous drop to 10% of the pretreatment values (Fig. 9). The remainder of the patients with malignant lymphoma had depressions of the mean lymphocyte values that were less than the response in polycythemia and must be considered more resistant than normal. We wondered whether the numbers of circulating lymphosarcoma cells in the peripheral blood of these patients before treatment might be related to radiosensitivity, but when the values were graphed after sorting the patients into two groups (those with lymphocyte counts above 4,000/mm^3, and those with counts less than this level) no differences in response could be detected. We found no clear relation between height of the initial lymphocyte count in CLL and the subsequent percentage fall with therapy. There is a slight suggestion that when the initial counts are low a somewhat exaggerated response may be anticipated. In general, however, from a clinical viewpoint, one cannot prescribe the amount of treatment needed on the basis of the height of the initial count.

Granulocytes

Granulocytes in chronic granulocytic leukemia begin to drop promptly and appear to be more sensitive to radiation than in other patients and in normal man. Mean values after 50 R can be superimposed on the responses of lymphocytes in lymphocytic leukemia even though we are comparing different cell types. However, the degree of change in granulocytic leukemia is related to the initial white cell level, a relation that does not exist for lymphocytic leukemia*. As noted earlier, leukocyte values were elevated in patients with polycythemia rubra vera before treatment, in some instances to a moderately pronounced degree. The drop after 100 R was less precipitous in PRV than in patients with chronic granulocytic leukemia, with a mild decrease during the first two weeks continuing to a nadir on day 42 in contrast to the response expected in normal persons. This depression from pretreatment values persisted for a number of months, although the pattern of climb toward pretreatment values varied considerably.

Platelets

Platelets usually reach their lowest level between the 21st and 35th days. In every group, responses to 100 R were significantly greater than to 50 R, and there was little overlap; 50 R produced little change in the patients with lymphoma, lymphocytic leukemia, and with chronic granulocytic leukemia. Individual variations were rather pronounced. Patients with polycythemia rubra vera who usually have moderate or high platelet values were not rebounding toward normal by the end of the six-week study period but had leveled off, remaining for many weeks or months at values considerably below the pretreatment ones (Fig. 16). This desirable effect from the point of view of therapy perhaps indicates that a new cellular steady state has been achieved either through the establishment of normal homeostatic mechanisms or depletion of stem cells to limiting levels of cell production.

SUMMARY

Eighty-nine treatments of total-body irradiation were given in single exposures of 50 R and 100 R at 1.5 R/min to patients with lymphoma, chronic leukemia, or polycythemia rubra vera. The clinical and hematologic responses during a 42-day study period were analyzed according to disease and dose; not unexpectedly the therapeutic responses varied. In lymphoproliferative disorders measurable clinical benefit did not depend solely on the radiation dose; the majority showed some shrinkage of enlarged lymph nodes, liver, or spleen, but the larger dose was not proportionally more effective in all cellular systems. Many required additional therapy within three months but this was not surprising in view of our use of only a single exposure. In granulocytic leukemia, improvement occurred in more than half of the patients. For polycythemia, the most clinically beneficial response appeared to be a decline of the dangerously elevated platelet counts to more normal levels that were maintained for many weeks or months.

The hematologic responses to 100 R usually but not invariably exceeded those to 50 R. A notable exception was the lymphocyte response of CLL in which the mean values of the responses of two groups were statistically the same. In general the abnormal proliferating blood elements did not return to pretreatment

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* This analysis is to be the subject of a separate report by J. Yuhas (ORNL), C. C. Lushbaugh, and T. Stokes (ORAU).

values in the same time sequence that is seen in recovery of normal cell lines in the acute radiation syndrome, suggesting that homeostatic mechanisms have been reestablished to hold the values within normal ranges. For example, elevated platelets in polycythemia rubra vera were depressed by the treatment but did not return toward normal by day 42, in contrast to events in lymphocytic leukemia where initial platelet levels are usually normal or low and recovery of platelet values is usually well under way by day 42.

The detailed graphs of blood cell values, together with their geometric means for each disease and exposure group form a useful reference for radiobiologic comparison with patterns in normal persons accidentally exposed, and relate the radiosensitivity of the various blood cell lines in the diseases studied.

The graphs also show the most probable or predictable response of the average patient with these diseases for 42 days after 50-R and 100-R exposure, providing a temporal course for comparing the relative effectiveness of similar total exposures of radiation given in small daily fractions at high or low dose rates. Such a comparative study of dose-rate effects upon therapeutic effectiveness is in progress.

Acknowledgements

This study represents a group effort of the clinical staff of the Medical Division with nurses, technologists, and physicians too numerous to mention. Special recognition should be given to Mary Smyser for accumulating and plotting the data, and to the Medical Illustrators, Cathy Stubbs and Jane Kimbro. The hematology technologists, Martha Clevenger, Joyce Hewins, Kathryn Lore, Shirley Colyer, and Mary Thomas performed with great care the innumerable procedures that form the backbone of the study. Dr. David White (present address: Centerville Clinic, Route 1, Fredericktown, Pa. 15333) with skill and dedication performed most of the follow-up clinical evaluations.

References

1. G. A. Andrews, B. W. Sitterson, A. L. Kretchmar, and R. Tanida, Studies of Total-Body Irradiation and Attempted Marrow Transplantation in Acute Leukemia, Acta Haemat. (Basel) 26: 129-153 (1961).

2. M. Brucer, The Acute Radiation Syndrome, A Medical Report on the Y-12 Accident, June 16, 1958, USAEC Report ORINS-25, April, 1959.

3. G. A. Andrews, B. W. Sitterson, A. L. Kretchmar, and M. Brucer, Accidental Radiation Excursion in the Oak Ridge Y-12 Plant. IV. Preliminary Report on Clinical and Laboratory Effects in the Irradiated Employees. Health Physics 2: 134-138 (1959).

4. G. A. Andrews, B. W. Sitterson, A. L. Kretchmar, and M. Brucer, Criticality Accident at the Y-12 Plant, in Diagnosis and Treatment of Acute Radiation Injury. Geneva. World Health Organization. New York. International Documents Service, 1961, pp. 27-48.

5. G. A. Andrews, Criticality Accidents in Vinca, Yugoslavia and Oak Ridge, Tennessee. Comparison of Radiation Injuries and Results of Therapy, JAMA, 179: 191-197 (1962).

6. T. M. Fliedner, G. A. Andrews, E. P. Cronkite, and V. P. Bond, Early and Late Cytologic Effects of Whole Body Irradiation on Human Marrow, Blood, 23: 471-487 (1964).

7. T. M. Fliedner, E. P. Cronkite, V. P. Bond, and G. A. Andrews, Mitotic Activity and Cytology of Human Bone Marrow After Accidental Exposure to Ionizing Radiation, in Proc. 7th Congress Europ. Soc. Hemat., London 1959, Part II, 1960, pp. 458-467.

8. G. A. Andrews, C. C. Lushbaugh, R. M. Kniseley, D. A. White, and B. I. Friedman, Haematological Effects of Whole-Body Irradiation in the Human Being, in IAEA Panel Effects of Ionizing Radiations on the Haematopoietic Tissue, International Atomic Energy Agency, Vienna, 1967, pp. 75-83.

9. E. E. Osgood, Treatment of Chronic Leukemias, J. Nucl. Med., 5: 139-153 (1964).

10. D. Walsh, Deep Tissue Traumatism From Roentgen Ray Exposure, Brit. Med. J., 2: 272 (1897).

11. R. E. Johnson, Evaluation of Fractionated Total-Body Irradiation in Patients with Leukemia and Disseminated Lymphomas. Radiology 86: 1085-1089 (1966).

12. W. H. Langham (Ed.), Radiobiological Factors in Manned Space Flight, National Academy of Sciences, Washington, 1967, pp. 76-90.

13. G. Brecher and E. P. Cronkite, Morphology and Enumeration of Human Blood Platelets, J. Appl. Physiol., 3: 365-377 (1950).

14. M. Brucer, A Total-Body Irradiator. Int. J. Appl. Radiat., 10: 99-105 (1961).

15. A. C. Morris, Jr., Measurements in a Total-Body Irradiation Facility, Int. J. Appl. Radiat., 11: 108-113 (1961).

16. R. L. Hayes, T. H. Oddie, and M. Brucer, Dose Comparison of Two Total-Body Irradiation Facilities, Int. J. Appl. Radiat., 15: 313-318 (1964).

17. R. E. Ellis, The Distribution of Active Bone Marrow in the Adult, Phys. Med. Biol., 5: 255-258 (1961).

18. P.-E. E. Bergner, Theory of Quantitative Radiation-Response Time-Data, USAEC Report ORAU-109, 1969.

19. Georges Mathé, Total Body Irradiation Injury: A Review of the Disorders of the Blood and Hematopoietic Tissues and Their Therapy, in Nuclear Hematology, E. Szirmai (Ed.), Academic Press Inc., New York, 1965, pp. 275-338.

20. V. P. Bond, T. M. Fliedner, and J. O. Archambeau, Mammalian Radiation Lethality, Academic Press Inc., New York, 1965.

21. V. P. Bond, E. P. Cronkite, R. S. Farr, and H. H. Hechter, Hematologic Observations, in Some Effects of Ionizing Radiation on Human Beings. A Report on the Marshallese and Americans Exposed to Radiation from Fallout and a Discussion of Radiation Injury in the Human Being, E. P. Cronkite, V. P. Bond, and C. L. Dunham (Eds.), USAEC Report TID-5358, July, 1956, pp. 43-63.

22. R. Schrek, S. L. Leithold, I. A. Friedman, and W. R. Best, Clinical Evaluation of an In Vitro Test for Radiosensitivity of Leukemic Lymphocytes, Blood, 20: 432-442 (1962).

TABLE A APPENDIX

RESPONSE TO 100 R METBI - POLYCYTHEMIA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x (approx. amt.)	Interval from last R_x to TBI	Spleen Change in Size	Systemic Symptoms + = Improvement	Pruritis + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to next R_x	Follow-up Interval (3)
1	F	62	3 mo.	Phlebot 6 x	1 mo.	N	NC	NC	Phlebotomy	2 yr. 4 mo.	4 yr. 6 mo.
2 a	F	73	1 mo.	None	-	- 2	NC	N	^{32}P 5 mc METBI 100 R Busulfan	3 mo. 23 mo. 3 yr.	4 yr.
2 b	F	75	3 yr.	METBI 100 R ^{32}P x 1	20 mo.	- 1	+ 1	N	Busulfan	13 mo.	2 yr.
3	F	64	$7\frac{1}{2}$ yr.	^{32}P x 1 Myleran Phleb. 25 x	$2\frac{1}{2}$ mo.	NC	+ 1	+ 1	Phlebotomy	7 mo.	4 yr.
4	M	55	15 yr	Phleb. 50 x 32P 7 x	6 mo. 6 mo.	NC	N	N	Phlebotomy	$4\frac{1}{2}$ mo.	4 yr.
5	M	68	6 yr. 7 mo.	Phleb. 15 x 32P 7 x	17 mo.	NC	+ 2	+ 2	None	-	D 1 yr. 7 mo.
6 (1)	M	59	1 mo.	None	-	-	+ 2	+ 2	LETBI 100 R LETBI 250 R	23 mo.	2 yr.
7 (2)	M	60	4 mo.	^{32}P 2 x	3 mo.	N	N	N	LETBI 150 R 2 x	15 mo.	2 yr.

(1) Splenectomy 4 yrs. earlier after abdominal trauma
(2) Primary thrombocythemia
(3) All patients alive at latest follow-up except patient 5; none with leukemia

Change in Size:
NC = No change - abnormal before and after treatment
N = Normal or absent before and after
+ 1 or + 2 = Larger
- 1 or - 2 = Smaller
Systemic Symptoms:
NC = No change - abnormal before and after treatment
N = Normal or absent before and after
+ = Improvement
- = Worse

TABLE B APPENDIX

RESPONSE TO 50 R CHRONIC GRANULOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size		Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
						Spleen	Liver				
1	M	67	3 days	None	-	NC	NC	+ 2	Ext. rad. to spleen Busulfan Splenectomy Hydrocortisone Prednisone Hydrocortisone	$2\frac{1}{2}$ mo. $5\frac{1}{2}$ mo. 14 mo. 14 mo. $14\frac{1}{2}$ mo. 15 mo.	D 15 mo.
2	M	48	3 days	None	-	- 2	- 1	+ 2	Ext. rad. to spleen Busulfan 6-MP	$2\frac{1}{2}$ mo. 6 mo. 2 yr. 1 mo.	D 2 yr. 3 mo.
3 a	F	52	5 days	None	-	- 1	- 1	+ 1	Busulfan METBI 50 R	1 yr. 4 yr. 4 mo.	D 6 yr. 7 mo.
3 b	F	57	4 yr. 4 mo.	METBI (50 R) Myleran	$8\frac{1}{2}$ mo.	NC	NC	NC	Ext. rad. to spleen Ext. rad. to liver 6-MP Prednisone Cyclophosphamide Methotrexate Hydrocortisone	9 mo. 18 mo. 23 mo. 23 mo. 2 yr., 3 mo. 2 yr., $3\frac{1}{2}$ mo. 2 yr., $3\frac{1}{2}$ mo.	D 2 yr. $3\frac{1}{2}$ mo.
4 a	F	60	34 days	None	-	N	N	+ 1	Busulfan METBI 50 R	3 mo. 3 yr.	D 5 yr. 7 mo.
4 b	F	63	3 yr. $1\frac{1}{2}$ mo.	METBI (50 R) Myleran	$1\frac{1}{2}$ mo.	NC	NC	NC	Ext. rad. to spleen Ext. rad. to liver METBI 100 R (See Table C, Case 2) Busulfan Prednisone 6-MP Hydrocortisone	2 mo. 9 mo. 11 mo. 13 mo. 2 yr. 5 mo. 2 yr. 5 mo. 2 yr. 7 mo.	D 2 yr. 7 mo.

TABLE B APPENDIX - Continued

Pt. No.	Sex	Age at ℞	Interval D_x to TBI ℞	Previous ℞	Interval from last ℞ to TBI	Change in Size		Systemic Symptoms + = Improvement	Subsequent Major Forms of ℞	Interval from TBI to Later ℞	Follow-up Interval
						Spleen	Liver				
5	M	59	1 yr. 9½ mo.	None	-	NC	NC	N	Ext. rad. to spleen Busulfan 6-MP Prednisone Hydrocortisone	2 yr. 10 mo. 3 yr. 8 mo. 3 yr. 10 mo. 3 yr. 10 mo. 3 yr. 10½ mo.	D 3 yr. 10½ mo.
6	F	53	1 mo.	None	-	NC	NC	+ 2	Ext. rad. to spleen (x 2) Ext. rad. to liver Ext. rad. to spleen (x 2) Hydrocortisone Prednisone 6-MP Prednisone	1½ mo.& 21 mo. 3 yr. 3 yr. 5 mo. & 4 yr. 3 mo. 4 yr. 9 mo. 4 yr. 9 mo. 4 yr. 10 mo. 4 yr. 10 mo.	D 4 yr. 10 mo.

TABLE C APPENDIX

RESPONSE TO 100 R CHRONIC GRANULOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R_x	Interval R_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size Spleen	Change in Size Liver	Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
1	F	64	4 yr	METBI 50 R (See Table B, Case 4) Myleran METBI 50 R (See Table B, Case 4) Ext. rad. to spleen Ext. rad. to liver	$2\frac{1}{2}$ mo.	NC	NC	+ 1	Busulfan Prednisone 6-MP Hydrocortisone	2 mo. 18 mo. 18 mo. 19 mo.	D $19\frac{1}{2}$ mo.
2	M	53	16 mo.	Cytoxan Ext. rad to liver Ext. rad. to spleen Ext. rad. to spine Ext. rad. to spleen x 2	$2\frac{1}{2}$ mo.	NC	NC	+ 1	Ext. rad. to rt. ilium Alkeran Ext. rad. to spleen 6-MP	$4\frac{1}{2}$ mo. 5 mo. 16 mo. $17\frac{1}{2}$ mo.	D $17\frac{1}{2}$ mo.
3	M	44	4 yr., 10 mo.	Ext. rad. to spleen x 8 Ext. rad. to liver Ext. rad. to spleen	6 mo.	NC	NC	- 2 (1)	Ext. rad. to spine	24 days	D 50 days
4	F	46	20 mo.	Ext. rad. to liver Ext. rad. to spleen LETBI 100 R	3 mo.	N	N	+ 2	METBI 100 R (divided dose)	5 mo.	A $13\frac{1}{2}$ mo.

(1) Paraplegia - terminal blastic state

Organ Size:
NC = No change - abnormal before and after treatment
N = Normal or absent before and after
- 1 or - 2 = Smaller
+ 1 or + 2 = Larger

TABLE D APPENDIX

RESPONSE TO 50 R CHRONIC LYMPHOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
1 a	M	67	3 yr., 8 mo.	^{32}P x 4	6½ mo.	- 2	N	- 2	+ 2	Chlorambucil Prednisone Ext. rad. to spleen ^{32}P x 2 METBI 50 R	6½ mo. 6½ mo. 10 mo. 2 yr., 4 mo.& 3 yr., 2 mo. 4 yr., 7 mo.	A 9 yr., 3 mo.
1 b	M	72	8 yr., 3 mo.	^{32}P x 4 METBI 50 R Chlorambucil Prednisone Ext. rad. to spleen ^{32}P x 2	17 mo.	- 1	NC	NC	+ 1	Prednisone	5 mo.	A 4 yr., 9 mo.
2 a	M	51	23 mo.	None	-	N	N	NC	N	Prednisone Ext. rad. to neck x 2 Chlorambucil ^{32}P x 4 Prednisone ^{32}P Ext. rad. to axilla Ext. rad. to axilla and groin METBI 50 R	9 days 14 days & 27 days 5 mo. 12 mo. 14 mo. 16 mo.& 21 mo. 22 mo. 23 mo. 2 yr., 1 mo. 2 yr., 2 mo. 2 yr., 9 mo.	D 6 yr. 4 mo.

TABLE D APPENDIX - continued

2 b	M	54	4 yr., 8 mo.	Prednisone Ext. rad. to neck x 2 Chlorambucil ^{32}P x 5 Prednisone Ext. rad. to axilla Ext. rad. to axilla and groin	7 mo.	+ 1	- 1	NC	+ 2	Chlorambucil Prednisone Ext. rad. to cervical nodes	3 mo., 3 mo. 3 yr., 5 mo.	D 3 yr., 8 mo.
3	M	71	3 days	None	-	NC	N	N	UD (1)	None	-	D 4 yr., 5 mo.
4	M	52	1½ mo.	None	-	NC	N	N	N	^{32}P x 3 Prednisone METBI 100 R Hydrocortisone Prednisone METBI 100 R (See Table E, Case 4) Hydrocortisone	4½ mo., 5½ mo., 17 mo. 22 mo. 2 yr. 2 yr., 2 mo. 2 yr., 4 mo. 3 yr., 4½ mo. 3 yr., 5 mo.	D 4 yr., 2 mo.
5	F	67	3 yr., 1 mo.	Prednisone Splenectomy Chlorambucil	11 mo.	- (absent)	- 2	- 2	+ 1 UD (2)	Prednisone Dexamethasone	14 d. 2½ mo.	D 2½ mo.
6	M	70	28 days	Ext. rad. to lymph nodes Chlorambucil	6 mo.	+ 1	- 1	NC	+ 1	Prednisone Hydrocortisone	1½ mo. 4 mo.	D 4½ mo.
7	M	55	6½ mo.	^{32}P x 2	6 mo.	N	N	- 2	+ 1	^{32}P	6 mo.	D 7 yr., 4 mo.

TABLE D APPENDIX - continued

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
8 a	M	68	3 days	None	-	+ 1	+ 1	- 1	NC	Prednisone METBI 50 R	5 mo. 3 yr., 5 mo.	D 6 yr., 7 mo.
8 b	M	71	3 yr., 5 mo.	METBI 50 R Prednisone	23 mo.	+ 1	+ 1	- 1	+ 1	Chlorambucil	15 mo.	D 3 yr., 2 mo.
9	M	74	5½ mo.	Prednisone 32p x 2	3 mo.(3)	N	N	- 2	+ 2	Prednisone Hydrocortisone	Cont. (3) 11 mo.	D 11 mo.
10	M	82	14 days	None	-	NC	NC	- 1	UD (4)	32p	2 mo.	D 1 yr., 2 mo.
11	M	63	14 days	Prednisone Hydrocortisone	(3) 7 days	- 2	UD	- 2	NC	Prednisone Hydrocortisone Ext. rad. to spleen	(3) Continuous 28 days 1 mo.	D 3 mo.
12	M	79	23½ mo.	METBI 100 R (See Table E, Case 15) Prednisone	- 18 days	- 1	NC	NC	+ 1	Prednisone Hydrocortisone Ext. rad. to spine Hydrocortisone Prednisone 6-MP Hydrocortisone	42 days 2½ mo. 3 mo. 5 mo. 5½ mo. 7 mo. 7½ mo.	D 7½ mo.

(1) Hospitalized for acute meningitis days 25 - 54
(2) Hospitalized with hemolytic anemia days 14 - 44
(3) On Prednisone during and after treatment
(4) Hospitalized with pneumonia days 35 - 45

TABLE E APPENDIX

RESPONSE TO 100 R CHRONIC LYMPHOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval From TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
1	F	40	2 mo.	Ext. rad. to spleen	11 days	NC	+ 1	- 2	N	Ext. rad. to abdomen 32p Prednisone Ext. rad. to neck & chest Ext. rad. to pelvis Ext. rad. to neck & rt. axilla Dexamethasone	3 mo. $4\frac{1}{2}$ mo. 7 mo. 15 mo. 2 yr., 6 mo. 2 yr., 10 mo. 5 yr.	D 5 yr., 9 mo.
2	M	49	2 yr., 1 mo.	TEM Ext. rad. to rt. axilla Ext. rad. to naso-pharynx Chlorambucil Ext. rad. to lt. axilla	12 mo.	NC	+ 1	NC	UD (1)	Prednisone 32p	2 mo. 4 mo.	D 3 mo.
3	F	49	3 days	Ext. rad. to neck and abd., axill. & ing. nodes	- 12 mo.	NC	NC	NC	NC	Prednisone Ext. rad. to liver Hydrocortisone	$1\frac{1}{2}$ mo. 2 mo. 4 mo.	D 4 mo.
4 a	M	54	2 yr., 2 mo.	METBI 50 R (See Table D, Case 4) ^{32}P x 3 Prednisone	$1\frac{1}{2}$ mo. (2)	- 1	- 2	- 2	NC	Hydrocortisone Prednisone METBI 100 R	2 mo. (2) $16\frac{1}{2}$ mo.	D 21 mo.
4 b	M	55	3 yr., 6 mo.	METBI 50 R (See Table D, Case 4) ^{32}P x 3 Prednisone METBI 100 R Hydrocortisone	3 days	+ 1	+ 1	NC	+ 1	Hydrocortisone Prednisone	11 days $1\frac{1}{2}$ mo.	D $4\frac{1}{2}$ mo.
5	M	88	4 yr.	Chlorambucil	1 mo.	N	N	+ 2	- 2	32p	$1\frac{1}{2}$ mo.	D 1 yr., $1\frac{1}{2}$ mo.

TABLE E APPENDIX - continued

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval From TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
6	M	57	6 days	None	-	+ 1	+ 1	NC	+ 1	32p Ext. rad. to neck Prednisone Hydrocortisone	3½ mo. 7 mo. 9 mo. 2 yr., 5 mo.	D 3 yr., 5 mo.
7	F	54	13 days	None	-	+ 1 ?	N	- 1	N	Chlorambucil Prednisone Dexamethasone Hydrocortisone Cortisone Acetate Splenenectomy	2½ mo. 4 mo. 2 yr., 2 mo. 3 yr., 4½ mo. 3 yr., 4½ mo. 3 yr., 4½ mo.	A 4 yr., 9 mo.
8 a	M	61	7 days	None	-	± 1	NC	NC	+ 2	METBI 100 R	22 mo.	D 2 yr., 2 mo.
8 b	M	63	22 mo.	METBI 100 R	22 mo.	- 1	NC	- 1	+ 1	Prednisone	2½ mo.	D 4½ mo.
9	F	82	1 mo.	None	-	N	N	N	NC	None	-	A 4 yr., 4½ mo.
10 a	M	74	3 days	None	-	N	N	- 1	N	METBI 100 R	18 mo.	D 3 yr., 9 mo.
10 b	M	75	18 mo.	METBI 100 R	18 mo.	N	N	- 1	+ 1	Ext. rad. to lt. ear LETBI 100 R LETBI 100 R Prednisone	8 mo. 16 mo. 21 mo. 2 yr.	D 2 yr., 3 mo.

TABLE E APPENDIX - continued

11	M	69	10 days	None	-	- 2	- 2	- 1	+ 1	Prednisone Hydrocortisone	9 mo. 3 yr., 4 mo.	A 4 yr., 1 mo.
12	M	76	1 mo.	Chlorambucil	18 days	NC	NC	NC	+ 1	Prednisone Hydrocortisone	2 mo. 4 mo.	D 4 mo.
13 a	M	61	14 mo.	Prednisone ^{131}I x 3 (3) ^{32}P x 3	$3\frac{1}{2}$ mo.	+ 1	+ 1	NC	+ 1	Ext. rad. to abd. Prednisone METBI 100 R	$2\frac{1}{2}$ mo. $8\frac{1}{2}$ mo. 12 mo.	D 3 yr., 8 mo.
13 b	M	62	2 yr., 2 mo.	METBI 100 R Ext. rad. to abd. Prednisone	1 mo.	N	NC	- 1	+ 1	Ext. rad. to ing. nodes Prednisone Cyclophosphamide Ext. rad. to lt. eye	9 mo. 15 mo. 21 mo. 2 yr., 4 mo.	D 2 yr., 8 mo.
14	M	71	18 days	None	-	- 1	- 1	UD	UD (4)	Prednisone Hydrocortisone	43 days $2\frac{1}{2}$ mo.	D $2\frac{1}{2}$ mo.
15	M	77	3 days	None	-	- 1	NC	NC	+ 1	Prednisone METBI 50 R (See Table D, Case 12) Hydrocortisone Ext. rad. to spine 6-MP	$7\frac{1}{2}$ mo. $23\frac{1}{2}$ mo. 2 yr., 2 mo. 2 yr., $3\frac{1}{2}$ mo. 2 yr., $6\frac{1}{2}$ mo.	D 2 yr., 7 mo.
16	M	55	4 days	None	-	- 1	- 1	- 2	+ 2	Prednisone	8 mo.	A 3 yr., 1 mo.

(1) Hospitalized 3 weeks post R_x for thrombocytopenia
(2) On Prednisone during and after treatment
(3) Toxic adenoma of thyroid
(4) At 6 weeks post R_x admitted for transfusions and Prednisone

TABLE F APPENDIX

RESPONSE TO 50 R METBI - LYMPHOSARCOMA

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from Last R_x to TBI	Change in Size			Systemic Symptoms + Improvement	Subsequent Major Forms of R_x	Interval From TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
1	F	37	12 days	None	-	NC	- 1	NC	+ 1	METBI 100 R (See Table G, Case 3 a)	3 mo.	D 4 yr.
										Splenectomy	13 mo.	
										METBI 100 R (See Table G, Case 3 b)	16 mo.	
										Ext. rad. to pelvic and abdominal nodes	21½ mo.	
										Prednisone	2 yr.	
										Nitrogen mustard	3 yr.	
										Ext. rad. to axillae	3 yr., 3 mo.	
										Vinblastine	3 yr., 6 mo.	
										Ext. rad. to lower abdominal mass	3 yr., 11 mo.	
										Hydrocortisone	3 yr., 11½ mo.	
2	M	42	19 days	None	-	?	?	- 1	N	Ext. rad. to ing. and iliac nodes	2 yr., 7 mo.	D 3 yr., 5 mo.
										METBI 100 R (See Table G, Case 13)	3 yr., 1 mo.	
										Ext. rad. to abd.	3 yr., 1½ mo.	
										Nitrogen mustard	3 yr., 2½ mo.	
										Chlorambucil	3 yr., 4 mo.	
										Prednisone	3 yr., 4½ mo.	
										Ext. rad. to mediastinum	3 yr., 5 mo.	

TABLE F APPENDIX - continued

3	M	46	2 yr., 3 mo.	Ext. rad. to neck & axilla 32P x 3	5 mo.	+ 1	N	- 1	NC	Chlorambucil Prednisone	5 mo. 7 mo.	D 3 yr., $2\frac{1}{2}$ mo.
4	M	72	17 days	None	-	N	- 1	- 1	NC	^{32}p x 3 Chlorambucil	2 mo. $13\frac{1}{2}$ mo.	A 4 yr., 10 mo.
5	M	45	10 mo.	Nitrogen mustard Ext. rad. to spleen Thio-Tepa	$8\frac{1}{2}$ mo. ?	+ 1	+ 1	+ 1	+ 1	Prednisone	2 mo.	A 2 yr., 1 mo.

TABLE G APPENDIX

RESPONSE TO 100 R METBI LYMPHOSARCOMA

Pt. No.	Sex	Age at R$_x$	Interval D$_x$ to TBI R$_x$	Previous R$_x$	Interval from last R$_x$ to TBI	Change in Size				Systemic Symptoms + = Im-provement	Subsequent Major Forms of R$_x$	Interval from TBI to Later R$_x$	Follow-up Interval
						Spleen	Liver	Lymph Nodes	Abd. Mass				
1 a	F	49	2 mo.	Ext. rad. to left inguinal nodes	1 mo.	N	- 1	- 2	0	N	Ext. rad. to sub-mandibular nodes 32p METBI 100 R	10 min. 11 mo. 21 mo.	D 4 yr., 9 mo.
1 b	F	51	23 mo.	Ext. rad. to left inguinal nodes METBI 100 R Ext. rad. to sub-mandibular nodes 32p	10½ mo.	N	N	- 2	- 1	+ 1	Ext. rad. to abdomen Nitrogen mustard Ext. rad. to spine Ext. rad. to rt. inguinal nodes Ext. rad. to rt. cerv. nodes Prednisone Ext. rad. to rt. thigh Ext. rad. to left pelvis 32p Hydrocortisone	2 mo. 5 mo. 5½ mo. 14 mo. 14 mo. 17 mo. 20 mo. 2 yr., 3 mo. 2 yr., 9 mo. 2 yr., 11 mo.	D 2 yr., 11 mo.
2	F	48	16 yr.	Ext. rad. to right cerv. nodes Ext. rad. to naso-pharynx Ext. rad. to left cervical nodes Ext. rad. to abd. Ext. rad. to right breast and axilla Nitrogen mustard	16 yr. 11 mo. 2 mo.	N	- 2	- 2	NC	(1)	None	-	D 2½ mo
3 a	F	38	3½ mo.	METBI 50 R (See Table F, Case 1)	3 mo.	+ 1	NC	- 2	0	N	Splenectomy METBI 100 R	10 mo. 13 mo.	D 3 yr., 8 mo.

TABLE G APPENDIX - continued

3 b	F	39	1 yr., 4½ mo.	METBI 50 R (See Table F, Case 1) METBI 100 R Splenectomy	3 mo.	-	NC	- 1	0	NC	Ext. rad. to pelvic and abd. nodes Prednisone Nitrogen mustard Ext. rad. to axillae Vinblastine Ext. rad. to abd. mass Hydrocortisone	5½ mo. 7½ mo. 19½ mo. 23 mo. 2 yr., 2 mo. 2 yr., 7 mo. 2 yr. 7½ mo.	D 2 yr., 7½ mo.
4	M	80	1 mo.	None	-	N	NC	- 1	0	- 1 (2)	Ext. rad. to mediastinum ^{198}Au to right pleural cavity Ext. rad. to mediastinum	1½ mo. 2 mo. 2½ mo.	D 6½ mo.
5 a	F	60	9 mo.	Ext. rad. to cheeks	8½ mo.	N	N	- 2	0	+ 1	METBI 100 R	12 mo.	D 4 yr., 2½ mo.
5 b	F	61	21 mo.	Ext. rad. to cheeks METBI 100 R	12 mo.	N	N	- 2	0	+ 1	Ext. rad. to rt. inguinal nodes Ext. rad. to rt. cervical nodes Ext. rad. to lt. femur & iliac nodes	3 mo. 13 mo. 2 yr., 7 mo.	D 3 yr., 2½ mo.
6	F	68	8 yr.	^{32}P x 4 Triethylenemelamine Ext. rad. to neck Ext. rad. to rt. axill. and inguinal nodes Ext. rad. to upper chest Ext. rad. to mediastinum	2 mo.	+ 1	NC	- 2	0	- 1 (3)	Ext. rad. to lt. axilla Ext. rad. to abd. mass Hydrocortisone	13 mo. 2 yr., 2 mo. 2 yr., 10 mo.	D 2 yr., 10 mo.
7 a	M	76	1½ mo.	None	-	N	- 1	- 1	0	N	^{32}P METBI 100 R	10 mo. 18½ mo.	D 22½ mo.

TABLE G APPENDIX - continued

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size				Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes	Abd. Mass				
7 b	M	78	20 mo.	^{32}p METBI 100 R	18½ mo.	UD	UD	- 2	- 1	N	Ext. rad. to abd. mass Nitrogen mustard Hydrocortisone	3½ mo. 4 mo. 4 mo.	D 4 mo.
8	M	49	10 days	None	-	N	+ 1	- 1	0	N	Ext. rad. to neck, axill. & ing. nodes Ext. rad. to rt. cervical nodes ^{32}p Prednisone Ext. rad. to iliac and inguinal nodes Ext. rad. to left axilla Ext. rad. to cheek Ext. rad. to spine Ext. rad. to spine Ext. rad. to thorax Ext. rad. to lt. cheek Cyclophosphamide	2 mo. 9½ mo. 13½ mo. 15 mo. 17 mo. 17½ mo. 3 yr., 2 mo. 4 yr., 9 mo. 5 yr., 5½ mo. 5 yr., 7 mo. 5 yr., 8 mo. 5 yr., 8½ mo.	A 5 yr., 10 mo.
9	M	87	53 days	None	-	N	N	NC (4)	0	NC	Ext. rad. to both ing. & iliac nodes Ext. rad. to neck nodes	28 d. 5½ mo.	D 6 mo.
10 a	F	55	1 mo.	None	-	N	- 2	- 1 (5)	0	+ 1	Ext. rad. to rt. clavicle Ext. rad. to lt. axilla	2 mo. 2½ mo.	D 4 yr., 9 mo.

TABLE G APPENDIX - continued

						-					Ext. rad. to rt. & lt. axillae Ext. rad. to neck METBI 100 R	10 mo. 10½ mo. 1 yr., 5 mo.	
10 b	F	57	1 yr., 6 mo.	METBI 100 R Ext. rad. x 4	6½ mo.	N	N	- 2	0	UD (6)	Prednisone Ext. rad. to neck Chlorambucil Ext. rad. to lt. chest Ext. rad. to rt. chest Ext. rad. to abdomen Hydrocortisone Cyclophosphamide	6 mo. 19½ mo. 20½ mo. 2 yr., 4 mo. 2 yr., 5 mo. 3 yr., 1 mo. 3 yr., 2 mo. 3 yr., 2½ mo.	D 3 yr., 4 mo.
11	F	55	3 mo.	None	-	N	N	- 2	0	NC	32p	6½ mo.	A 5 yr., 2 mo.
12	M	72	5 days	None	-	N	- 2	- 1	0	+ 1	32p Ext. rad. to rt. iliac & ing. nodes Ext. rad. to abdomen Dexamethasone Prednisone Hydrocortisone	2¼ mo. 4½ mo. 5½ mo. 12 mo. 18½ mo. 20 mo.	D 21 mo.
13	M	45	4 yr., 1 mo.	METBI 50 R (See Table F, Case 2) Ext. rad. to ing. & iliac nodes	- 5½ mo.	N	N	NC	NC (7)	NC	Ext. rad. to abdomen Nitrogen mustard Chlorambucil Prednisone Ext. rad. to mediastinum	16 d 2 mo. 3 mo. 3½ mo. 4 mo.	D 4 mo.

TABLE G APPENDIX - continued

Pt. No.	Sex	Age at R_x	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size				Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval from TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes	Abd. Mass				
14	M	78	1½ mo.	None	-	N	- 1	- 1	0	+ 1	Ext. rad. to sacrum Prednisone	8 mo. 20 mo.	D 21 mo
15	M	78	3 mo.	None	-	- 1	- 1	- 1	0	+ 1	LETBI 100 R Chlorambucil Prednisone Cyclophosphamide Hydrocortisone	15 mo. 22 mo. 23 mo. 2 yr., 3½ mo. 2 yr., 4 mo.	D 2 yr., 4 mo.
16	M	76	4 yr., 1 mo.	Ext. rad. to neck & both axillae Nitrogen mustard Ext. rad. to neck, both axillae, and mediastinum Ext. rad. to abdomen x 3 Local rad. sq. Ca cheek Methylprednisolone Triethylenemelamine Prednisone	(8)	N	NC	- 1	0	UD (8)	Prednisone Ext. rad. to keratoses Cortisone Acetate	(8) 1½ mo. 5½ mo.	D 5½ mo
17	M	68	4 mo.	None	-	- 1	NC	- 2	0	+ 1	Cyclophosphamide Ext. rad. to sq. Ca face Ext. rad. to met. Ca pelvis	9 mo. 10 mo. 2 yr., 9 mo.	A 2 yr., 9 mo.

(1) In terminal condition at time of R_x
(2) In hospital with bilateral pleural effusion days 31-81 post R_x
(3) In hospital with pneumonia days 21-66 post R_x
(4) No regression at day 14. External radiation at day 28
(5) Maximum regression at 4 weeks, enlarging again by 6 weeks
(6) In another hospital with herpes zoster at 6 weeks
(7) External radiation to abdomen on day 16. No change at day 42
(8) On Prednisone during and after treatment

TABLE II APPENDIX

RESPONSE TO METBI - HODGKIN'S

Pt. No.	Sex	Age at R_x	Dose	Interval D_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval From TBI to Later R_x	Follow-up Interval
							Spleen	Liver	Lymph Nodes				
1	F	21	50 R	1 mo.	None	-	N	N	- 1	N	Ext. rad. to supraclavicular and mediastinal nodes Nitrogen mustard Ext. rad. to axillae Ext. rad. to clavicular nodes Ext. rad. to axillae Nitrogen mustard Ext. rad. to mediastinum Ext. rad. to spine Uracil Mustard Ext. rad. to breast mass Ext. rad. to abd. mass Vinblastine Ext. rad. to left neck Cytoxan in right chest cavity Ext. rad. to right chest Ext. rad. to right iliac nodes	1½ mo. 17 mo. 2 yr., 2½ mo. 3 yr., 1 mo. 3 yr., 9 mo. 5 yr., 1 mo. 5 yr., 3 mo. 5 yr., 8 mo. 5 yr., 9 mo. 7 yr., 1 mo. 7 yr., 7 mo. 7 yr., 11 mo. 8 yr., 3 mo. 8 yr., 5 mo. 8 yr., 5 mo. 8 yr., 6 mo.	A 8 yr., 10 mo.
2	F	65	100 R	14 d.	None	-	N	N	- 1 (1)	NC (1)	None	-	D 14 d.

TABLE II APPENDIX - continued

Pt. No.	Sex	Age at R$_x$	Dose	Interval R$_x$ to TBI R$_x$	Previous R$_x$	Interval from last R$_x$ to TBI	Change in Size			Systemic Symptoms + - Improvement	Subsequent Major Forms of R$_x$	Interval From TBI to Later R$_x$	Follow-up Interval
							Spleen	Liver	Lymph Nodes				
3	F	20	100 R	21 d.	None	-	N	N	- 1	NC	Nitrogen mustard	$1\frac{1}{2}$ mo.	D 2 yr., $3\frac{1}{2}$ mo.
											Prednisone	2 mo.	
											Ext. rad. to supraclav. nodes and mediastinum	$2\frac{1}{2}$ mo.	
											Ext. rad. to mediastinum & left axilla	$7\frac{1}{2}$ mo.	
											Ext. rad. to lt. neck	$7\frac{1}{2}$ mo.	
											Ext. rad. to rt. axill. & supraclav. nodes	$12\frac{1}{2}$ mo.	
											Nitrogen Mustard	14 mo.	
											Vinblastine	17 mo.	
											Ext. rad. to abdominal mass	2 yr.	
											Ext. rad. to left axilla & mediastinum	2 yr.	
											Uracil Mustard	$2\frac{1}{2}$ yr.	

(1) Last seen at 2 weeks after R$_x$

TABLE J APPENDIX

GEOMETRIC MEANS (% PRETREATMENT)

Values of the Computed Geometric Means Used in the Hematologic Figures of this Report

Day

Disease	R	Blood Value	1	2	4	7	14	21	28	35	42	49	56	62	76	84	No. Pts.	Fig. No.
CLL	50	WBC (all)	94.3	79.0	65.2	56.5	45.6	39.8	44.3	41.6	34.8						15	
		WBC (good response)	96.0	80.5	60.2	52.2	39.0	32.5	35.9	32.4	26.5						11	1
		WBC (poor response)	89.8	74.9	81.2	70.5	69.8	69.7	79.1	82.3	68.3						4	1
		Absolute Lymphs (all)	94.3	79.4	63.1	54.4	42.9	34.6	36.2	34.6	31.9						15	
		Abs. Lymphs (good response)	96.9	81.7	58.4	50.0	36.5	27.2	26.6	25.4	23.7						11	3
		Abs. Lymphs (poor response)	87.7	73.5	78.1	68.4	67.2	66.9	78.1	81.0	66.9						4	3
		Platelets	114.1	97.9	100.4	90.5	86.3	67.0	65.0	78.2	92.0						15	4,6
	100	WBC (all)	86.1	74.3	58.4	46.3	38.1	35.0	29.7	32.6	30.7						20	
		WBC (good response)	78.1	65.4	48.4	35.2	28.1	22.4	19.7	21.2	21.0						14	2
		WBC (poor response)	97.7	96.2	87.0	81.4	74.9	85.2	78.4	65.1	59.5						5	2
		Abs. Lymphs (all)	82.2	69.3	54.2	42.3	34.9	30.0	28.2	27.7	26.7						19	
		Abs. Lymphs (good response)	77.2	60.6	47.3	33.3	26.2	20.4	19.3	20.3	19.5						14	3
		Abs. Lymphs (poor response)	97.9	101.3	77.3	82.6	78.0	88.5	76.3	62.3	60.6						5	3
		Platelets	94.0	81.6	81.6	81.6	75.4	40.5	25.2	26.8	38.4						20	5,6

TABLE J APPENDIX - continued

Disease	R	Blood Value	Day 1	2	4	7	14	21	28	35	42	49	56	62	76	84	No. Pts.	Fig. No.
Lymphoma	50	WBC	86.56	93.9	86.78	77.07	67.58	70.21	64.55	68.55	61.75						5	
		Absolute Lymphs	92.8	81.1	76.8	69.7	59.3	72.2	72.1	77.4	69.4						5	
		Platelets	97.7	102.3	104.8	105.6	131.6	85.6	70.9	87.1	92.6						5	
	100	WBC	91.1	81.7	74.5	66.1	80.1	81.1	66.5	53.5	53.1						20	7
		Absolute Lymphs	77.7	79.9	59.2	50.0	73.4	65.1	57.9	59.5	57.6						20	8
		Platelets	95.2	94.0	88.7	93.2	82.4	52.7	27.3	28.6	42.8						22	10
CGL	50	Hgb	99.6	98.9	95.7	95.1	96.9	101.0	101.4	102.4	105.2						8	
		Absolute Lymphocytes	68.6	59.0	64.3	52.4	49.4	58.4	77.3	57.9	76.8						8	
		WBC	90.81	80.47	68.91	55.38	48.58	45.25	50.66	46.58	43.09						8	11, 15
		Platelets	101.9	96.6	104.0	103.7	136.5	101.7	81.5	91.8	92.9						8	13, 15
	100	Hgb	97.7	99.2	95.5	93.7	103.3	108.7	109.8	104.8	102.0						4	16
		Absolute Lymphocytes	99.3	111.7	82.9	80.7	48.5	73.8	65.6	58.8	63.8						4	
		WBC	98.7	93.6	68.5	35.2	22.8	17.8	23.9	26.9	17.3						4	12, 15
		Platelets	100.6	91.8	123.7	111.8	111.5	75.6	58.7	69.9	48.5						4	14, 15
PRV	100	Hgb	99.1	98.2	96.4	96.0	95.6	95.8	97.0	95.1	96.5	96.7	98.7	102.4	109.9	106.1	8	20
		Hct*	49.2	48.7	47.9	46.5	46.9	46.5	45.8	45.3	45.5	46.5	46.7	49.0	49.1	47.6	8	21
		MCHC	99.4	99.8	99.5	101.4	100.3	100.9	104.0	102.9	104.7	103.9	104.3	98.1	105.8	105.1	8	22
		WBC	-	85.1	85.0	80.1	73.4	47.1	46.2	29.7	26.7	38.0	35.8	-	40.0	55.6	7	17
		Absolute Lymphs	-	72.4	77.2	65.1	68.1	-	56.4		44.4						7	18
		Platelets	98.2	101.9	107.3	100.0	95.5	49.4	28.6	29.2	39.4	43.9	40.3	-	50.9	52.4	8	19

* Absolute values rather than percent pretreatment.

Dr. **Heyssel**. It was my understanding and it remains my understanding that externally given low or chronic doses and large doses really was not expected to have a greater, much greater effect than, for instance, the use of phosphorous 32, which is given intermittently also in these diseases or other kinds of therapy available at that time. It didn't appear likely, and as a practical matter I think in 1966 in a program I reviewed the same comment was made.

On the other side of the coin, it needs to be remembered that diseases being treated, chronic lymphocytic leukema, lymphosarcoma, chronic granulocytic leukemia, polycythemia Rubra Vera, were not diseases that were amenable to any therapy at that time except for over a period of time really palliative therapy.

So in that sense a different kind of approach and different delivery of radiation was perfectly rational as far as we were concerned, certainly as likely to be as effective as anything else the patient was treated with.

Mr. **Gore**. Now you conclude in your review that the retrospective study on human exposure remains "a highly important and meritorious endeavor." This was in 1970, I am sorry, the year before your formal review.

Dr. **Heyssel**. Right.

Mr. **Gore**. Did the committee conclude that the prospective studies were equally meritorious or did you see it in that context?

Dr. **Heyssel**. I do not think we saw it in that—well, I guess it depends on how you read the words we said at the time. And I guess I can quote directly from the committee report at that time: "The controlled attempts therefore to determine the effects of optimal total dose and optimal dose rates of radiation to be used in control of these diseases are justified," which I guess would imply that a prospective study was appropriate; and further, that it appeared from the data presented that the survival of patients is as good this way as any other way, and finally noted we felt interim statistical evaluation of the program in a formal sense would be useful to the staff as well as the committee. So I think we said two things: That it ought to be evaluated where it is at this point and, given what we know at this point, it is appropriate to proceed on a prospective basis.

Mr. **Gore**. Well, the real nub of this issue is whether or not the desire to acquire data, either of general radiobiological interests or for NASA's specific needs took precedence over the treatment of patients, or caused medical decisions which were not optimum for the patients. I am sure in conducting your review that was the principal question you addressed. What was your conclusion?

Dr. **Heyssel**. Our conclusion, and I will quote directly from the report:

> In the Cincinnati program, one of the major issues raised was Department of Defense support of studies. We think the situation at Oak Ridge is quite different. While NASA funds are involved for evaluation of the effects of total body radiation, the selection of patients for the program and their continuance in the program is clearly in the hands of a clinical group who is responsive to patient care needs and to the need for optimal therapy as opposed to the needs of the investigative protocol of NASA.

I can only say from reading that that we must have thought about that a good deal and must have been convinced at the time that that was correct.

Mr. **Gore**. How many people were on the committee?

Dr. **Heyssel**. There were, at that time, in 1972, there were six people on the committee.

Mr. **Gore**. How many of them were from Oak Ridge?

Dr. **Heyssel**. None of them.

Mr. **Gore**. None of them were from Oak Ridge?

Dr. **Heyssel**. No.

Mr. **Gore**. How many of them were associated with the research done there, none of them?

Dr. **Heyssel**. To my knowledge, none of them.

Dr. Grahn was from Avgonne National Laboratories in Chicago; Dr. Greenlaw was a nuclear medicine expert from Marshfield Clinic, totally unrelated; Dr. Shields Warren on the committee was, I guess, the most prominent radiation biologist in the country at that time, the late Dr. Warren, and was from New England Deaconess Hospital, Tufts New England Medical Center; Dr. Winn was a surgeon interested in radiation from Massachusetts General Hospital; Dr. Coniglio was a biochemist from Vanderbilt University interested in lipid chemistry and very well known for that, and myself. While I had collaborated in research at Oak Ridge, certainly by 1971 I was well removed from any interaction with Oak Ridge.

I think it is fair to say that it was, perhaps with the possible exception of its chairman, me, a fairly distinguished group of people who could I think be objective about these things.

Mr. **Gore**. Were any of the members of the committee also involved in human experimentation with radiation?

Dr. **Heyssel**. Certainly Dr. Grahn, Dr. Greenlaw, and I think Dr. Winn were.

Mr. **Gore**. So three of the six were?

Dr. **Heyssel**. And I had been very directly. Actually, when I got to Hopkins I was continuing some research.

Mr. **Gore**. OK. Mr. Shamansky?

Mr. **Shamansky**. Thank you, Mr. Chairman.

Doctor, in 1967, the establishment of the human use committee, I would indicate to me that the question was in the minds of people doing this kind of work, as to—whether or not there should be standards for human experimentation; is that a fair statement?

Dr. **Heyssel**. I think that is a fair statement, sir.

Mr. **Shamansky**. And it seems to me reasonable to assume that that was based on their own experience with their human subjects.

Dr. **Heyssel**. I think it was based on not only that, but real concern about the use of all sorts of human subjects, prisoners as an example, students; the issue of the freedom of information and consent was there for I think everybody to be concerned about. It is a fact, I think, that the thrust came first from the FDA to institutionalize that, and then through NIH research grants. But in general, in the institutions at least that I am familiar with and associated with, there was not resistance to that, there was recognition that it was needed.

Mr. **Shamansky**. Assuming you remember, that same attitude existed at Oak Ridge?

Dr. **Heyssel**. Yes; I think it did.

Mr. **Shamansky**. As far as you could tell?

Dr. **Heyssel**. Yes, sir.

Mr. **Shamansky**. Based on the testimony that you have heard and what you now know about the particular case of Dwayne Sexton, is there anything inconsistent with a responsible approach to human experimentation and what we apparently know happened in this case?

Dr. **Heyssel**. Sir, I walked in toward the end of that testimony, so I am really not familiar with all the details.

Mr. **Shamansky**. Sure.

Dr. **Heyssel**. If you could be specific as to what was done, I might be able to help you.

Mr. **Shamansky**. Sure, in the work of the first committee—I am assuming you did not specifically refer to this particular case.

Dr. **Heyssel**. No; we did not.

Mr. **Shamansky**. And you didn't refer to any particular cases at all?

Dr. **Heyssel**. In 1967 we simply convened to agree on a process and a procedure for review of human experimentation by some sort of committee structure. We did not at that time really review any specific experimental procedures.

Mr. **Shamansky**. At what time of the year in 1967 did you do this?

Dr. **Heyssel**. I have it here.

Mr. **Shamansky**. Was it April?

Dr. **Heyssel**. It was either April—I believe it was April, yes, sir.

Mr. **Shamansky**. So these standards or procedures were being discussed at Oak Ridge in April?

Dr. **Heyssel**. April 6, 1967.

Mr. **Shamansky**. And I believe our testimony was the boy expired in December of——

Mr. **Gore**. 1968.

Mr. **Shamansky**. December 1968. Do you know if Oak Ridge had adopted any Associated Universities Medical Division standards with respect to human experimentation?

Dr. **Heyssel**. Yes, sir. I know that not from personal experience but from a detailed description of what occurred in terms of institutional review boards and so forth, and I believe anyone receiving NIH grants and so forth had to adopt such procedures within the next couple of years.

I have no reason to believe, in other words, that the recommendations made in 1967 were not carried out.

Mr. **Shamansky**. OK.

Then the question would be, which we would have to determine then is, in fact, were those procedures followed in this particular case?

Dr. **Heyssel**. Yes, sir.

Mr. **Shamansky**. Based on your experience—do you work in the field of leukemia and the treatment of leukemia?

Dr. **Heyssel**. Sir, I do not any more. I was active in it in 1967, last in 1968; since that time——

Mr. **Shamansky**. Did you hear any testimony with respect to the treatments available to Dwayne Sexton and the prospect that he would have at the time of his last relapse?

Dr. **Heyssel**. I didn't hear enough of the testimony to be able to comment on it.

Mr. **Shamansky**. Thank you.

What is your understanding of the overall survival rates in the country for this kind of leukemia that we described?

Dr. **Heyssel**. I assume that we are talking about acute lymphoblastic leukemia in a child?

Mr. **Shamansky**. Yes.

Dr. **Heyssel**. In 1960 to the midsixties or to almost 1970, the prospect and inducing a remission in a child with what would have at that time been conventional chemotherapy, 6-Mercoptopurine, aminopterim, and prednisone with the beginning use of the vincristine and multiple chemotherapies given at one time, was very high, in the neighborhood of probably 70 to 80 percent. I am picking numbers out of my head from a distant past at this point.

However, the cure rate, no one was really seriously talking about significant numbers of cures. Prolonged remissions were known, but the experience wasn't really there. So, we had all had the experience of seeing this remarkable event occur, in which a child, and a few adults, with acute leukemia would have what would appear to be a perfectly normally functioning bone marrow and then the devastation of watching it turn around.

The second time around, the chances of inducing a remission were reduced considerably from the kind of numbers I was talking about.

Mr. **Shamansky**. How about the fifth or sixth time?

Dr. **Heyssel**. Very, very unlikely, both then and today.

Mr. **Shamansky**. Is it your professional opinion that if a patient has had five or six remissions but then had an obvious relapse, a serious relapse, what would be the prognosis for that child?

Dr. **Heyssel**. It would be very poor.

Mr. **Shamansky**. Very poor.

Did you ever review the levels of radiation that were being used in this particular case?

Dr. **Heyssel**. In the case of Dwayne Sexton?

Mr. **Shamansky**. Yes.

Dr. **Heyssel**. No, sir.

Mr. **Shamansky**. Would you know one way or the other that they were unusual or not unusual at the time?

Dr. **Heyssel**. If you can tell me the dose, I might be able to.

Mr. **Shamansky**. They are low energy.

Mr. **Gore**. 353 roentgens.

Mr. **Shamansky**. Total body radiation?

Mr. **Gore**. Total body irradiation.

Dr. **Heyssel**. Well, of course very few people were doing total body radiation at that point with the exception of attempts, some beginning attempts at bone marrow transplantation with total body radiation. That is a dose which certainly would severely damage and probably kill many leukemic cells and it is probably, depending on dose rates and so forth, on the tolerable side with regard to gastrointestinal and other kinds of effects, so I think that there was not usual—at that time. I think a lot of things were being tried because it was a pretty hopeless situation.

Mr. SHAMANSKY. Given the condition of the patient, this was the fifth or sixth relapse——

Mr. GORE. If my colleague will yield, that was the testimony of our first witness but I think that the medical records indicate that the doctors identified three specific occurrences that they identify as relapses. There may be some definitional problem here.

Mr. SHAMANSKY. Let's take three to avoid any dispute.

Would such an exposure to that radiation be contraindicated under those circumstances?

Dr. HEYSSEL. If the judgment—first off, the experience clearly was that following the first remission and the first relapse, your ability to induce a remission with further chemotherapy then available declined precipitously. And as a consequence, if the judgment of the physicians at that time was that that child probably was not going to receive further benefit from chemotherapy and something else might be tried, that, it seems to me, would have been a rational judgment.

I would imagine the same child today would probably undergo total body radiation, but with a bone marrow transplant, a fairly common approach to that problem now.

Mr. SHAMANSKY. Given the situation at that time and what was known, would it be your opinion that this was not unreasonable?

Dr. HEYSSEL. No, sir, it would not be, I would think, unreasonable.

Mr. SHAMANSKY. As long as it was consciously known that it was experimental?

Dr. HEYSSEL. That is correct.

Mr. SHAMANSKY. Without representations that it was, in fact, a verified and established treatment?

Dr. HEYSSEL. That is correct.

Mr. SHAMANSKY. Thank you.

Mr. GORE. Other witnesses will address those specific questions at the end of our witness list today.

Let me ask you a couple of more brief questions.

If you knew that a patient had a staph infection on the day of irradiation, would that alter your decision to proceed?

Dr. HEYSSEL. It depends on the—that is, Congressman, a complicated question. It depends on, one, the kind of staph; two, where the staph infection is located; three, if this were an individual, for instance, that you might be—well, I can't think of any good reasons to ever give anybody radiation, but if it is a child or someone else who essentially at this point has a nonfunctioning bone marrow and probably has altered immune defenses, it probably wouldn't be the controlling factor, the fact that there was a staph infection there.

Mr. GORE. What about the use of the same facility to irradiate animals on alternate days or during the mornings and then humans in the afternoon? What about that? Did you look at that in your review?

Dr. HEYSSEL. I don't remember that we did and we may well have. It is not mentioned in any of the reports. The issue there obviously would be the fear of contamination in the sense of, perhaps, infections. If, however, proper precautions were taken in handling the animals, I would see no major problem with that.

Mr. **Gore**. Without objection, we will put the text of that portion of your 1972 review which deals with the total body irradiation program in the record at this point.

[The information follows:]

Appendix A
86th Board Mee

Report of the Medical Program Review Committee

Oak Ridge Associated Universities Summary Meeting - 1972

The Oak Ridge Associated Universities Medical Division Pro Review Committee met officially March 29th and 30th. The preli session for planning was held on the evening of March 28th. Al members of the Committee were able to be present for the review and included Dr. John Coniglio, Vanderbilt University, Nashvill Tennessee; Dr. Robert Greenlaw, Marshfield Clinic, Marshfiled, Wisconsin; Dr. Douglas Grahn, Argonne National Laboratory, Chic Illinois; Dr. Robert Heyssel, Johns Hopkins Medical Institutio Baltimore, Maryland (Chairman); Dr. Shields Warren, New England Deaconess Hospital, Boston, Massachusetts; Dr. Henry Winn, Massachusetts General Hospital, Boston, Massachusetts.

General Comments Concerning the Review Process

The Committee found the time spent at the Medical Divisio of Oak Ridge Associated Universities an enjoyable period. While the Committee did "work" and did take its responsibilities to th Medical Division and Oak Ridge Associated Universities seriously, it was pleasurable "work" activity as a result of the genuine in actions with the staff of the Medical Division. These interact were made possible through the cooperation and willingness of a personnel to discuss frankly the strengths and weaknesses of the various parts of the program. Moreover, the Committee is grate for the positive response to our suggestions of last year to make available earlier the draft of the Annual Report for review prior to coming to Oak Ridge as well as materials from the Director with regard to the overall program objectives of the Medical Division, budgetary information, and the document pertaining to long-range issues of scientific and administrative nature with which the Medical Division is concerned. The Committee recognizes the considerable effort which was expended to make these materials available but believes that they made possible a more objective and responsive review. The general format of the Committee's visit works well and the program review of major projects conducted by the staff was well done. That coupled with the opportunity for the various members of the Committee to spend lengthy periods of time in the afternoon with the staff is a most satisfactory way of conducting the review. It was particularly useful to sit down after the program review at lunch with Drs. Andrews and Kniseley.

Review of Major Projects

1. Marmoset Chimerism - In its review in 1971, the Committee expressed some concern with this project in terms of both its short and long-term productivity. Those same concerns exist in 1972. The Committee does recognize that Oak Ridge Associated Universities and the Medical Division have developed a special committee to evaluate the program and the Committee looks forward to their findings. The Committee also appreciates the fact that

this program has received funding from NIH for studies in chimerism in marmosets and that a competing renewal grant will be applied for this year. In a real sense it is an issue of judgment as to whether study of the Marmoset, a unique primate in terms of twinning and chimerism, can provide unique answers in terms of immunologic systems and, if so, whether it can be accomplished at a reasonable cost. It would be helpful to the Committee to have a specific outline of goals, objectives and questions to be asked and answered. It clearly is not in the purview of the Committee to either suggest or make a decision with regard to this project, but it is an area which we are pleased to see is being examined closely by the Medical Division and ORAU.

2. Radiation Immunology and Transplantation - The program in Radiation Immunology has real strengths and in the judgment of the Committee is a very solid program. On the one hand, it engages in necessary basic research on the effect of radiation on the immunologic apparatus and develops approaches to transplantation and, on the other hand, it provides support for the human transplantation and the total body radiation programs. The systematic study done on the effect of dose and dose rate on immune processes coupled with anti-human lymphocyte globulin, which have indicated that a twenty-four hour period after radiation is an optimal time for administ

of marrow, has given new insights into approaches to transplantation. Extension of these real strengths into the areas of labeling of tumor-specific humoral antibodies and development of in-vitro radioimmunoassay techniques would be a natural development of these investigations and could grow out of the program which exists if the resources are available. Moreover, the latter studies have the potential of extending the strengths of the Medical Division in the area of development of radio-pharmaceuticals and perhaps toward in vivo localization of isotopes for diagnostic scanning and/or therapeutic purposes.

3. Marrow Transplantation Project - The ability to produce apparent bone marrow grafts in two of two patients over the last two years using the protocol of radiation combined with anti-lymphocyte globulin and chemical suppression of the immune apparatus is impressive. These exceedingly difficult studies are well worth pursuing in the careful and controlled manner which the staff has employed to date. It is hoped that in time and with more experience, that it will be possible to define a balance point at which the graft could survive without a graft versus host reaction and without the distressing problems of infection. While the recurrence of leukemia compounds the difficulties with the study, the Committee agrees with the staff, i.e., that the hazards of bone marrow transplantation are such that these studies really must be confined to patients whose short-term outlook is such that desperate

and even heroic measures are justified.

4. Total Body Radiation - This is a major component of the resear effort. It is appropriate for the Committee at this point to comment on the ethical nature of such studies in view of ques raised concerning studies done at the University of Cincinnat The Committee believes that the studies done at Oak Ridge in patients with chronic myeloproliferative disorders, i.e., chr granulocyte leukemia and polycythemia rubra vera and lymphoproliferative disorders, chronic lymphocytic leukemia and lymphosarcoma do not constitute a departure from standard accepted and effective therapy in these diseases, except in terms of manner of administration and the controlled nature of the studies. Radiation has been a main stay of therapy in these diseases for decades and whole body radiation, intravenously administered radioisotopes such as ^{32}p and radiatio to restricted sites have all been accepted therapy and in many respects still are. While chemotherapy is efficacious, it is not ideal in all cases and for one reason or another can't be used in others. The controlled attempts, therefore, to determine the effects of optimal total dose and optimal dose rates of radiation to be used in control of thes diseases are justified. It appears to the Committee from the data presented, moreover, that the patients are not disadva by the procedure since the survival rate appears to be as good as with other methods of treatment. The Committee does feel that an interim statistical evaluation of the program is

the formal sense would be useful to the staff as well as the Committee.

In the Cincinnati Program one of the major issues raised was Department of Defense support of the studies. Again, we think the situation at Oak Ridge is quite different. While NASA funds are involved for evaluation of effects of total body radiation, the selection of patients for the program and their continuance in the program is clearly in the hands of a clinical group who is responsive to patient care needs and to the need of optimal therapy as opposed to the needs of the investigative protocol of NASA.

This program has great importance in terms of the potential of understanding of fatigue in radiation injury - an extension of previous biochemical studies related to radiation injury. It is of interest that the physiologic monitoring studies which have been implemented indicate that fatigue is not related to increased pulmonary impedance and is not associated with EKG changes or changes in heart rate. In that regard, it was pointed out in the Committee session that fatigue also occurs after local radiation, such as head and neck radiation, a much smaller volume of tissue, and perhaps this might be pursued along with the studies in total body radiation. It was felt that earlier biochemical studies done in acute radiation injury following total body exposures probably could fruitfully be pursued again, since a whole variety of enzymes can now be measured which were not measured in the original studies. A marked increase has already been noted in CPK following irradiation exposure at Oak Ridge. Perhaps measurement of lactic dehydrogenase, the transaminases, as well as a variety of other constituents of the blood and urine which can now be done would be worthwhile.

Finally, it was pointed out that these studies done at Oak Ridge, combined with gathering of information from other places concerning acute radiation injury and attendant symptoms in terms of their variability and time of onset, have really been the basis upon which NASA planned the radiation safety guidelines for the Apollo Lunar Exploration Program. As was indicated earlier, these latter studies have never been the prime intent, but they nevertheless proved to be an important by-product of the investigation of the uses of radiation in the treatment of illness.

5. Biological Chemistry Project - This is a program of high quality and it is clear that Dr. Snyder has moved to bring it closer to the clinical programs in radiation injury. The ability of the program to attract outside grant support speaks quite directly to its quality in terms of peer evaluation of the projects. The program is excellent evidence of the wisdom of allowing talented people the opportunity to pursue lines of investigation which appear to have little direct bearing on the overall program content. Their studies, which have el

the importance of either linked lipids in cancer cells, the relative absence of this pathway in normal cells, and the manner in which tritium atoms from these ethers can be introduced specifically into cancer cells offer the exciting possibility of new therapeutic approaches. Even if this proves not feasible, an important biochemical approach to micro-dosimetry and study of the effect of radiation on cell membranes is of considerabale importance. The study on plasmalogens is obviously of considerable importance. The personnel in this program are to be highly commended and encouraged to continue their "scientific pioneering" adventures.

6. Tumor Localization with Gallium - This project has been pursued aggressively in the past year. In the opinion of the Committee, the development of a cooperative group and the agreement upon the elements of data collection in an attempt to get standardization of instrumentation and interpretation of the scans are extremely important. With only minor exceptions in the past, this sort of effort has not been put forth for new agents for diagnosis, not only in nuclear medicine but in other fields. This program has a potentiality, therefore, of serving as a model in evaluation of radiopharmaceuticals in succeeding years. The Committee feels that such efforts cannot be held together by the enthusiasm and voluntary participation of the various centers involved in such a study alone but require funding

for those centers if these efforts are to be expanded into other areas. We believe the potential of this sort of appro is so great that perhaps other agencies, such as the Nationa Cancer Institute where applicable or the FDA, would appear to have much to gain from helping to fund the effort. The work done which clearly indicates the lysozomal location of gallium is of high quality and importance. The technical aspects were obviously carried out with great skill, and aga can serve as a model leading to greater understanding of localization of isotopes and to microdosimetry.

Finally, the efforts of the group in radiation health physics to develop a catalog which would allow others ready accesss to human dosimetry from internally administered isotopes deserves support.

The Committee believes that the work on gallium might be considered as the beginning of expanded work on the development of radiopharmaceuticals by the Medical Division of Oak Ridge Associated Universities, an area which in coming years should develop rapidly.

7. Cytogenetic Project - This program is obviously of tremendou importance to the transplantation and whole body radiation It is gratifying that the program was able to attract outsi grant support, which in turn makes it possible to have a pr of this quality at the Medical Division. The longitudinal

studies of chromosomal aberration frequency in a controlled group and a group on contraceptive drugs are of great interest. The striking variations shown in the controls in the months of March, April and May on an annual basis now for over two years raises a series of interesting questions. We hope these can be pursued over time.

8. Computer Technology - The question raised by the Committee is whether at this time computer technology should be developed further and how it should be developed. If the efforts of the Division are expanded in radiopharmaceutical development and dosimetry, the Committee believes that the need for more resources in the area of computer technology will be necessary. The Committee does recommend that a profesionally trained programmer/analyst be hired in place of the part-time, partially trained personnel presently engaged. This will be especially critical if computer applications are to be expanded.

General Comments Concerning Long-Range Issues and Plans

In general, we feel the ideal solution to a hospital program ight well be to tie it in some manner to the Oak Ridge Hospital. e recognize the difficulties involved in this, and the fact that ertain facilities, such as radiation facilities, the whole body ounter and laminar airflow rooms, cannot be relocated realistically. e support the idea of trying to develop a Cancer Research Center n East Tennessee with participation by the Medical Division in such n activity. The need for a full-time radiotherapist is not uestioned. The two new areas proposed, i.e., involvement in valuation of a radio-protective compound and Carbon-11 studies, oth look like promising avenues to explore.

Mr. GORE. Now, are you familiar with the rather harsh and critical review completed by the Atomic Energy Commission in 1974?

Dr. HEYSSEL. Of?

Mr. GORE. Of the medical division.

Dr. HEYSSEL. No, sir; I have not seen that.

Mr. GORE. Did you identify any trends in the clinical setting or procedures during the time that you reviewed it?

Dr. HEYSSEL. Well, as I indicated earlier, I had been familiar with the Oak Ridge Institute of Nuclear Studies and Oak Ridge Associated Universities operations there since 1959, at least.

In 1959 and the early part of the sixties, in a sense, almost, Oak Ridge Institute of Nuclear Studies invented the use of radioisotopes diagnostically in medicine.

Many very innovative ideas came from there. They were deeply involved in the development of radiopharmaceuticals for use in medicine and for diagnosis. It is no accident that Abbott Laboratories, which was one of the larger suppliers through the sixties and probably still today of radiopharmaceuticals, originally was established almost next door to ORINS there. So I am describing an institution that made major contributions to nuclear medicines early in the sixties.

The climate changed. They trained a lot of people, myself included, who went back to universities; the NIH was being very generous in those days. One could get grants. I would think a great deal of the research and development work subsequently shifted to the university laboratories and away from Government-run laboratories or Government-funded laboratories, totally funded such as ORINS.

Over that period of time I think that the productivity probably did decline at the laboratory, both in nuclear medicine and other things, although even when we were reviewing them, they were the first to use gallium, which was subsequently to become an important scanning agent.

In a sense though, they had a monopoly in the late fifties and early sixties, and that was gone by the early seventies. There were a lot of other people out there scrambling to do important things.

Mr. GORE. So what you are saying is that over the years you observed this institution, certain trends appeared. During the early years it was ahead of the game and producing innovative techniques that later saved many lives, but because of changes in the nature of the research effort in the United States, and possibly because of some of the other factors that you mention in your review, the cutting edge of new procedures began to appear elsewhere and the description that you applied to the medical division changed in the later years.

Dr. HEYSSEL. I think that is fair. I think that looking at the medical division over a fair period of time, I hardly know of any committee report that I have looked at that did not find criticism, and many of us were concerned about its relative isolation from other institutions. Oak Ridge is where it is because it is a little isolated, across the mountain, as you know, Congressman Gore. And that was a concern.

There was another concern, which was the clinical facilities available to it and the patient population for doing clinical research. I think all those things had an impact on the productivity of the laboratory over a fair period of time; yes, sir.

Mr. **Gore.** All right. I would like to thank you very much for appearing here today and giving us the benefit of a rather unique perspective on these events.

Mr. **Gore.** I would like to call now a large panel of witnesses, and while I am doing so I would ask them to work their way forward and we will take a minute or two break while you are coming forward. I will read the names.

Dr. Charles W. Edington, Acting Associate Director, Office of Health and Environmental Research; Dr. Nathaniel F. Barr, manager, health and environmental risk analysis programs, Office of Health and Environmental Research; Dr. William R. Bibb, Director, Research Division, Oak Ridge Operations Office; Dr. William W. Burr, former Deputy Assistant Secretary for Environment and former Director, Office of Health and Environmental Research, Department of Energy; and Andrew J. Stofan, Acting Associate Administrator for Office of Space Science, NASA.

Gentlemen, if you wouldn't mind raising your right hand and taking the oath.

[Oath read.]

Dr. **Edington.** I do.

Dr. **Barr.** I do.

Dr. **Bibb.** I do.

Dr. **Burr.** I do.

Mr. **Stofan.** I do.

Mr. **Gore.** All right. Thank you very much.

I might say for those following the hearings that this panel is going to respond to questions about the institutional arrangement between AEC, now DOE, and NASA, and related questions, and then the next panel consists of the medical personnel at Oak Ridge Associated Universities, who were directly responsible for the experiments in question, the treatments in question.

Without objection, the prepared statements of all of our witnesses on this panel will be put into the record in full at this point and I would invite our witnesses to proceed with the presentation of any or all of their statements if they see fit.

Dr. Edington, if you would begin. Welcome.

TESTIMONY OF DR. CHARLES W. EDINGTON, ACTING ASSOCIATE DIRECTOR, OFFICE OF HEALTH AND ENVIRONMENTAL RESEARCH; DR. NATHANIEL F. BARR, MANAGER, HEALTH AND ENVIRONMENTAL RISK ANALYSIS PROGRAMS, OFFICE OF HEALTH AND ENVIRONMENTAL RESEARCH; DR. WILLIAM R. BIBB, DIRECTOR, RESEARCH DIVISION, OAK RIDGE OPERATIONS OFFICE; DR. WILLIAM W. BURR, FORMER DEPUTY ASSISTANT SECRETARY FOR ENVIRONMENT AND FORMER DIRECTOR, OFFICE OF HEALTH AND ENVIRONMENTAL RESEARCH, DEPARTMENT OF ENERGY; AND ANDREW J. STOFAN, ACTING ASSOCIATE ADMINISTRATOR FOR OFFICE OF SPACE SCIENCE, NASA

Dr. EDINGTON. Thank you, Mr. Chairman. I am pleased to be here as the Acting Associate Director for the Office of Health and Environmental Research in the Department of Energy.

Mr. GORE. If you could pull the microphone a little closer so we can hear you.

Dr. EDINGTON. Yes, sir. As you probably are aware, the Office of Health and Environmental Research has its roots in the Division of Biology and Medicine that was created in 1947 by the AEC. At that time the Division of Biology and Medicine supported two research programs. One was to determine the effects of exposure to ionizing radiation, both biological and environmental, and the other program was to conduct research and development of the beneficial applications of radiation and radionuclides in the diagnosis and treatment of human diseases.

Those two programs continue today in the Office of Health and Environmental Research. In the transition from AEC to ERDA, now DOE, our mission in the effects research area has broadened to include effects associated with all energy technology developments.

Other than that, we still continue our research in the radiation area.

Our research is basically supported in the GOCO facilities, the Government-owned, contractor-operated facilities, such as the National Laboratories, and specialized biomedical and environmental research laboratories, of which the Oak Ridge Associated Universities is one. We also support research at universities, research institutions, and other organizations such as hospitals.

The research is supported by what we call management contracts. Headquarters staff in Washington are responsible for program and policy guidance. The day-to-day management of the laboratory activities, including the scientific details, is the responsibility of the laboratory. To assist them in their research activities, the laboratories usually have their own research advisory committees. Periodically, however, the Office of Health and Environmental Research conducts in-depth peer reviews of those laboratories to insure scientific quality, productivity, and relevance to the mission of the organization.

When radiation was used for medical purposes, it was a routine medical practice, I think, in the period of the sixties for the patient to be informed by his physician of the reasons for and the purpose of treatment.

Furthermore, no proposed treatment protocol by an individual physician could be used without approval of all the clinical staff. In fact, in November 1966, the Advisory Committee for Biology and Medicine recommended to the AEC that formal procedures be established in AEC laboratories to insure that ethical practices were followed with respect to human use.

In December of 1966, Dr. Charles L. Dunham, then Director of the Division of Biology and Medicine, directed the program directors of the laboratories to consider current laboratory practices and revise their procedures, if necessary, to comply with the code of ethics which the Surgeon General had instituted.

Subsequently, in 1970, Dr. Totter, then Director of the Division of Biology and Medicine, notified the laboratories that the AEC had officially adopted the National Institute of Health procedures which were described in the booklet entitled "Protection of the Individual as a Research Subject." At an early time, therefore, the AEC and its laboratories were cognizant of and sensitive to the need for implementation of procedures to insure a responsive code of ethics in their research programs.

Because of the nature of our facilities and the outstanding quality of their scientific programs, the DOE laboratories have been involved for a long time in research for other Federal agencies. In the present fiscal year, approximately $75 million in research is being supported by other agencies at the DOE laboratories.

In 1961, NASA needed all available information on biological effects of radiation for their planning of manned space missions. Dr. Dunham wanted to be sure that all relevant information was available to NASA and that they were aware of the expertise and facilities which existed at our laboratories. At that time Dr. Barr, on my right, was assigned as the AEC coordinator for this activity.

Over a period of years, a number of tasks were identified and research projects were initiated at the various laboratories. One of these tasks was initiated in 1964 at the Oak Ridge Institute for Nuclear Studies. The objective was to compile and analyze information on human health effects resulting from accidental or therapeutic exposure to large doses of ionizing radiation.

In addition, data which was being obtained following whole body treatment of cancer patients at ORAU, an ongoing AEC clinical project, was also provided as a part of the NASA project. NASA continued to support this data collection and analysis project until 1974 when both the NASA project and the AEC-supported whole body therapy progarm were terminated.

Mr. Chairman, this concludes my testimony. I will be happy to try to respond to questions.

[The prepared statement of Dr. Edington follows:]

Statement By

Charles W. Edington
Acting Associate Director
Office of Health and Environmental Research
Office of Energy Research
U.S. Department of Energy

Mr. Chairman, I have a brief statement which I shall summarize and submit for the record. The other members of the Panel will have additional statements. The DOE Office of Health and Environmental Research had its origin in the Division of Biology and Medicine which was created by the Atomic Energy Commission in 1947. As a part of the Atomic Energy Commission, the Division of Biology and Medicine was responsible for two different research programs. In one of the programs, support was provided for a broadly based research effort to determine the biological and environmental effects resulting from exposure to radiation. In the other program, support was provided for research and development of beneficial applications of radiation and radionuclides for use in diagnosis and treatment of human disease (the Nuclear Medicine program). With the transition from AEC to ERDA and now DOE, these two programs continue; however, our mission has broadened to include support for research to determine the biological and environmental effects associated with all energy technology developments. Research is carried out at the Government-owned, Contractor-operated (GOCO) National Laboratories and several specialized biomedical and environmental research laboratories, of which the Oak Ridge Associated Universities (ORAU) is one. In addition, research is supported by contract at universities, hospitals and other research institutions. The contracts at the GOCO facilities are management-type contracts. In such contracts, policy and program guidance is the responsibility of Headquarters staff. The contractors submit scientific proposals and budget requests for research programs each year to the Department. These research programs and budget submissions are reviewed by Headquarters technical staff who have the responsibility for overall management, coordination and scientific quality of the research program; however, they are not involved in the day-to-day supervision of the work which is carried out at the laboratories. That supervision is the responsibility of laboratory management. To assist them in management of their research programs, the laboratories have their own scientific advisory committees. To ensure that the research programs remain productive and scientifically excellent, periodic indepth, peer reviews are conducted at each of the laboratories by the Office of Health and Environmental Research.

When radiation was used for medical purposes in the 1950's and 1960's at ORAU, it was routine medical practice that the patient was informed by his physician of the reasons for and purpose of the treatment. Furthermore, no proposed treatment protocol by an individual physician could be used without approval of all the clinical staff. In November 1966, the Advisory Committee for Biology and Medicine recommended to the AEC that formal procedures be established in AEC laboratories to ensure that ethical practices were followed with respect to human use. In December 1966, Dr. Charles L. Dunham, Director of the Division of Biology and Medicine, directed the Program Directors of the laboratories to consider current laboratory practices and revise their procedures, if necessary, to comply with the code of ethics which the Surgeon General had instituted. Subsequently, in 1970, Dr. John R. Totter, then Director of the Division of Biology and Medicine, notified the laboratories that the AEC had officially adopted the National Institutes of Health procedures which were described in the booklet entitled "Protection of the Individual as a Research Subject." At an early time, therefore, the AEC laboratories were cognizant of and sensitive to the need for implementation of procedures to ensure a responsive code of ethics in their research programs.

Because of the nature of their facilities and the outstanding quality of its scientific programs, the DOE laboratories have been involved for many years in research for other Federal agencies. In the present fiscal year, approximately $75 million in research is being supported by other agencies at the laboratories. In 1961, NASA needed all available information on biological effects of radiation for their planning of manned space missions. Dr. Dunham wanted to be sure that all relevant information was available to NASA and that they were aware of the expertise and facilities which existed at our laboratories. Dr. Barr was assigned as the AEC coordinator for this activity.

Over a period of a few years, a number of tasks were identified and research projects were initiated at various AEC laboratories. One of these tasks was initiated in 1964 at the Oak Ridge Institute for Nuclear Studies. The objective was to compile and analyze information on human health effects resulting from accidental or therapeutic exposure to large doses of ionizing radiation. In addition, data which was being obtained following whole body treatment of cancer patients at ORAU, an ongoing AEC clinical project, was also provided as a part of the NASA project. NASA continued to support this data collection and analysis project until 1974 when both the NASA project and the AEC-supported whole body therapy program were terminated.

Mr. Chairman, this concludes my testimony. My colleagues and I will be happy to answer any questions which you may wish to ask.

Mr. GORE. Thank you very much.

We will hold our questions until the other members of the panel have completed their statements.

Dr. Barr, if you could go next.

Dr. BARR. Yes, Mr. Chairman.

In early 1961, shortly after I joined the Division of Biology and Medicine of the Atomic Energy Commission, Dr. Charles Dunham, the Division Director, asked me to assist staff of the National Aeronautics and Space Administration in their efforts to obtain, organize, and utilize information on the biological effects of ionizing radiation for the purpose of planning and conducting manned space missions. Consideration of this matter was stimulated by the identification and characterization of the van Allen radiation belts surrounding the Earth and by observation of increased particle fluxes in these belts subsequent to the detonation of a nuclear explosion in space.

Dr. Dunham wanted to assure that relevant information compiled over several decades was available to NASA mission planners, and that they were acquainted with ongoing programs and facilities at AEC contractor laboratories which might be of assistance to them. Discussions with representatives from various NASA program offices, begun in early 1961, led to the identification of several areas of common interest and, over a period of several years, to the initiation of a number of programs funded by NASA at AEC contractor-operated laboratories.

In 1964, these various projects were consolidated under a basic interagency agreement between NASA and AEC. Approximately a dozen tasks ranging from improved characterization of the ionizing radiation environment in space to experimental observations of the biological effects of ionizing radiation under conditions of weightlessness were included under this agreement. All were devoted to reducing uncertainties regarding the potential health impacts associated with exposures of astronauts to ionizing radiations during manned space missions.

In mid-1964, task 9 was initiated under this agreement at the Oak Ridge Institute for Nuclear Studies. The objective of this task was to identify and compile information on effects observed in humans exposed to large doses of ionizing radiation either accidentally or in the course of therapy for disease, and to organize and interpret this information to support NASA's responsibilities for planning and conducting manned space flights.

A portion of this information was to come from observations made on patients exposed to whole body radiation in the course of therapy for malignant diseases at the Oak Ridge Institute for Nuclear Studies. This was an ongoing program funded by AEC to evaluate the value of such therapy. Administrative supervision and technical monitoring of task 9 were the responsibility of Drs. Sherman Vinograd and Edward McLaughlin, who worked under Dr. George Nauf, Head of Aerospace Medicine in NASA's Office of Manned Space Flight.

Drs. William Burr and William Bibb were responsible, under Dr. Dunham, for administration and management of the AEC-funded therapy evaluation program, and Dr. Gould Andrews was responsible for the conduct of this program. Dr. Clarence Lushbaugh was principal investigator for the NASA-supported work conducted under task 9. Both these programs continued with their independent objectives essentially unchanged until terminated in 1974.

That concludes my statement, Mr. Chairman.

[The prepared statement of Dr. Barr follows:]

Statement By
Nathaniel F. Barr
Manager, Health and Environmental Risk Analysis Programs
Office of Health and Environmental Research
Office of Energy Research
U.S. Department of Energy

Mr. Chairman,

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Mr. **Gore**. Thank you very much.

I would like to hear now from Dr. Bibb, Director of the Research Division at the Oak Ridge Operations Office.

Dr. **Bibb**. Mr. Chairman, I have a fairly long statement which is to some extent quite historical. I thought it would be useful to trace the course of the AEC program through the years to get to some of the questions the committee asked, particularly as they relate to the facilities and how they came into being.

Dr. Heyssel has eloquently and succinctly stated what he saw as some of the medical accomplishments. With your permission, I would like to discuss the evolution of ORINS/ORAU and not delve too much into the NASA involvement issue since Dr. Barr just discussed that.

Mr. **Gore**. We will put the entire text in the record and you can proceed in any fashion you wish. If you want to summarize it and just give a history of the Oak Ridge operation, please do so.

Dr. **Bibb**. As Dr. Barr pointed out, when I worked in Washington I was a technical representative responsible for monitoring the AEC-funded research at the ORINS/ORAU Medical Division. My supervisor was Dr. Burr.

Shortly after the AEC was created, it was determined that there would be three hospitals created; one of them would be located at the Argonne Cancer Research facility operated by the University of Chicago, one at Oak Ridge, and one at Brookhaven National Laboratory.

I will focus on the hospital that ultimately came to be located in Oak Ridge. At that time, the AEC had a contract with the Oak Ridge Institute of Nuclear Studies. The purpose of that contract was to have the contractor train scientific personnel from institutions throughout the country in the use of radioisotopes and to arrange for graduate students and university faculty members to go to Oak Ridge to participate in research programs.

In addition, ORINS performed another function, which was to make it possible for faculty at the University of Tennessee to train scientists in Oak Ridge. In February 1948, the Division of Biology and Medicine asked ORINS to consider the feasibility of establishing and operating an Oak Ridge clinical research facility. In March 1948, ORINS convened a meeting of the representatives of each southern medical school to determine the feasibility of establishing such a clinical research facility in Oak Ridge to use the exceptional research tools available there for the study of neoplastic disease.

At the end of the conference, a recommendation was made to AEC that ORINS proceed with the proposed clinical facility to be housed in an unused wing of the AEC-owned and contractor-operated community hospital. Following approval of the ORINS proposed operating plan by AEC, construction of a laboratory building and renovation of the adjacent existing hospital wing was begun.

ORINS appointed Dr. Marshall H. Brucer as chairman of the Medical Division. In May 1950 the first patient was admitted to the Medical Division. The floor plan of the original clinical facility operated by ORINS is shown in figure 1 of my prepared testimony. For reference purposes, the location of the AEC community hospital is also shown.

During the early fifties, the ORINS Medical Division developed methods of synthesizing radio-labeled compounds and preparing them for clinical trials. Early attempts at radioisotope therapy were largely unsuccessful. At the same time that internally administered therapeutic radioisotopes were being studied, ORINS was also conducting an active program to develop external radioisotope sources to be used instead of X-rays to produce an external beam that could be directed into the body as a treatment for cancer.

By late 1951, an efficient cobalt-60 teletherapy machine had been designed and placed in a specially built room at ORINS. After testing, it was moved to M. D. Anderson Hospital in Houston for clinical trials. Early in 1952, the ORINS Medical Division began a teletherapy evaluation program to determine which of several potentially useful radioisotopes would prove most useful in teletherapy. Cobalt-60 became the most widely used teletherapy source, and before long this form of therapy was common all over the world.

During that period, radioiodine-131 had become available from Oak Ridge National Laboratory and, as a result, numerous clinics throughout the United States were using it for the diagnosis and treatment of thyroid cancer. Unfortunately, there was no uniformity in methods used to measure the administered dose or the amount of radioisotope localized in the thyroid gland.

In 1954, ORINS initiated a radioiodine uptake calibration program. Several fashion store mannequins were purchased and artificial thyroid glands with accurately known levels of mock iodine were placed in their necks. These calibration kits were sent from one laboratory to another around the country where each clinician used his own instruments to measure the thyroid dose and uptake of the mannequin. All results were reported back to the Medical Division where they were compared with expected values.

As anticipated, there were wide discrepancies from the standard in the results obtained. Through collaboration between Oak Ridge National Laboratory and ORINS a new instrument was designed which soon became widely available commercially and made radioiodine thyroid diagnosis and treatment a reliable and standard clinical procedure.

The Medical Division also devoted a major effort to human total body irradiation studies to improve the treatment for certain types of leukemia and lymphoma. Prior to 1960, the total body irradiation was given to the patients using a cobalt-60 teletherapy unit.

In June 1958, eight workers at the AEC Y-12 plant in Oak Ridge were involved in a radiation accident. Their doses ranged from 23 to 365 rads, with five of the men receiving more than 225 rads. All of the men were treated at the ORINS Medical Division and subsequently recovered.

As a result of the Y-12 accident, it became clear that more information on the response of humans to radiation was needed. The film badges worn by the workers were unreliable indicators of actual exposure, and a biological measure of exposure was needed to aid the clinician in handling such cases.

Dr. Gould Andrews, who began his career at ORINS in 1949 as chief of hematology, developed a special interest in the hematologic effects of radiation and studied the Y-12 men over the next 21 years. He also developed an acute interest in the hematologic response of patients exposed to total body irradiation therapeutically to better learn how to predict and treat these effects in exposed workers. As a result of this knowledge, Dr. Andrews was usually called to consult at other institutions where accidents had occurred.

The ORINS Medical Division was the designated hospital for handling any radiation accident at the AEC plants in Oak Ridge. The AEC expected that hematologic data from patients being treated with total body irradiation, in addition to being used to benefit other patients, would also benefit any radiation accident victim.

In 1960, the new Oak Ridge Hospital was completed and the patients moved out of the AEC Community Hospital. The old hospital was renovated and the ORINS Medical Division patients moved into this renovated facility.

The teletherapy machines available in the late 1950's did not give uniform radiation fields such as one would prefer for total body radiation therapy. During irradiation treatment using teletherapy, the patient had to be moved to try and provide for a fairly uniform exposure. To solve this problem, ORINS designed and constructed a new facility which was a concrete shielded room containing eight radiation sources that delivered a uniform dose to the patient.

This facility, called medium exposure total body irradiator [METBI], was completed in 1959 and began operation in 1960. In the METBI facility, patients would lie on a bed located in the center of the room during radiotherapy. Radiation sources were operated remotely and the patient was monitored visually by specially arranged mirrors at the control panel in an adjacent room. The patient was able to communicate with the technician during treatment by means of an intercom system.

Figure 2 is a schematic of the ORINS Medical Division in 1968 showing the renovation to which I have just referred, and including the whole-body counter and LETBI facilities.

In 1960, an immunology program was started at ORINS to study the effects of radiation on immune responses and the immunology of bone marrow transplantation. In order to study the types of infections that occur in patients with bone marrow damage from radiation and chemotherapy, a research program in microbiology was initiated in 1960.

In late 1961, Dr. Brucer retired as chairman of the ORINS Medical Division and the following year Dr. Gould Andrews was appointed as his successor.

AEC was the Federal agency responsible for developing the basic biological knowledge for use by other organizations and institutions in developing radiation protection standards. Thus, it was normal for the National Aeronautics and Space Administration to approach AEC in 1963 for assistance in determining the biological risks astronauts might encounter during space travel.

Under the AEC-NASA interagency agreement existing at that time, the project was assigned to ORINS Medical Division by AEC. Following a feasibility study in which medical records at ORINS were examined to determine if useful data could be obtained from patients' charts, the ORINS study was expanded to 45 hospitals and eventually included radiobiologic information from over 2,500 therapeutic exposures. The results of this initial study were made available to the National Academy of Sciences and were published in 1967 in "Radiobiological Factors in Manned Spaceflight."

As a result of animal studies on repair mechanisms, it was becoming obvious that radiation delivered at a slower rate had the potential for providing the same therapeutic benefit to the patient without causing the undesirable side effects observed at faster rates. However, to get the same dose, the patient would need to be exposed for much longer periods of time, such a facility, to become known as the low exposure total body irradiator [LETBI], to test this idea in a clinical environment was proposed by ORINS to AEC in 1965.

At the time LETBI was first proposed to AEC, ORINS suggested that in addition to the clinical studies for AEC, subsequent analysis of the stored data might be of value to NASA. For the AEC, LETBI was intended to provide information on the possible benefit of low-dose-rate total body irradiation as opposed to the more conventional higher dose rate facilities.

The construction of LETBI was funded by AEC to provide this information in a one-of-a-kind facility. If LETBI had proven more beneficial than conventional methods, this concept would have been expected to be picked up by other clinical centers using whole body irradiation for cancer therapy. Since LETBI did not prove to be more beneficial than conventional means, only one such facility was constructed by AEC.

The low exposure total body irradiation [LETBI] facility provided a comfortably furnished inner room 16 feet square in which there was an almost uniform radiation field. The radiation sources were positioned in a larger, outer, heavily shielded room. Patients were able to move about comfortably during irradiation periods prolonged over several days. The exposure rate was 1.5 r/hour or 60 times less than that of the METBI facility.

Equipment was installed for watching for undesirable side effects and for measuring and recording various physical changes of patients during irradiation. An IBM 1800 computer was used to provide on line monitoring and analysis of physiologic changes much as in a modern intensive care unit. In 1965, this was state-of-the-art instrumentation and AEC relied on NASA for the knowledge they had acquired in developing such instrumentation for astronaut monitoring. The monitoring equipment in LETBI cost $65,000 and was funded by NASA.

With the completion of the Low Exposure Total Body Irradiator [LETBI] in 1967, it became possible to collect continuous patient monitoring data during long exposure periods to low-dose-rate radiation. Although the elaborate physiological monitoring was designed to monitor the patient continuously during treatment, it was also possible to simultaneously preserve the same data on tape for subsequent analysis. The storage and analysis of patient data collected as part of the AEC-funded LETBI program was beyond the scope of the AEC program and all AEC costs for this activity were reimbursed by NASA. It should be emphasized that all activities related to the clinical treatments using the LETBI facility were funded by AEC.

In January 1966, ORINS underwent a name change to the current Oak Ridge Associated Universities.

By the early 1970's, it was becoming clear that while the treatment of patients at the ORAU Medical Division was excellent, the number of cases treated was too small to be statistically significant in evaluating certain modalities of therapy. Moreover, since all costs related to patient care were borne by AEC, it was becoming increasingly difficult to justify the continued operation of this and other AEC hospitals.

Whereas in the early fifties and sixties these AEC hospitals were responsible for developing the whole new field of nuclear medicine, by the late sixties their influence had spread and nuclear medicine was well-advanced at most major medical centers. Physicians who had been trained at these AEC hospitals had returned to their universities and were now conducting the training. The AEC hospitals had in effect put themselves out of business.

Mr. GORE. The implication of that is that the reason it was closed was that they had done their job, completed it. Yet your agency, in explaining its position to close it at the time in 1974, listed a variety of other reasons that are not mentioned or referred to in your statement. I assume that we will have an opportunity to cover that in the questions.

Dr. BIBB. I hope so, Mr. Chairman.

Mr. GORE. OK.

Dr. BIBB. The clinical cancer research program was terminated in 1974 with the closing by AEC of the inpatient care facility. In 1975, Dr. C. C. Lushbaugh became the chairman of the newly named ORAU Medical and Health Sciences Division. Following the closing of the clinical inpatient facility, the building was again renovated.

When the decision was made to close the hospital, all patients who had participated in the cancer treatment program were offered the option for continued treatment by private physicians in Oak Ridge or hospitalization in the Oak Ridge Hospital of the United Methodist Church. In the former, AEC would reimburse any difference in costs between their insurance and the doctor's fees. In the latter, AEC would pay any charges over and above those the patients' insurance would pay. DOE continues to pay some of the costs for care of the former patients.

Mr. Chairman, that concludes my statement.

[The prepared statement of Dr. Bibb follows:]

Statement By

William R. Bibb, Director
Research Division
Oak Ridge Operations Office
U. S. Department of Energy

Mr. Chairman and members of the Committee: My name is William Bibb. I am Director of the Research Division at the Department of Energy's Oak Ridge Operations Office. From 1965 until 1970, I was a member of the Medical Research Branch, Division of Biology and Medicine of the Atomic Energy Commission in Germantown, Maryland.

As a member of the Medical Research Branch, I was the technical representative responsible for monitoring the AEC funded research at the ORINS/ORAU Medical Division. My supervisor was Dr. William Burr, Jr.

The various operations of the Atomic Energy Commission involved the production and handling of large amounts of radioactivity. Associated with these operations was potential and actual exposures of the workforce to radiation. In recognition of the potential hazards of such exposures, the Atomic Energy Commission and its predecessor, the Manhattan Engineering District, had, from the beginning, conducted research programs designed to enhance basic understanding of the nature of these exposures and of the associated biological risk.

The Biomedical Research Program of the AEC was conducted through the Division of Biology and Medicine. The general objectives of the program were:

1. Increased knowledge of the biological effects of radiation in order to provide basic information to those concerned with developing radiation protection standards.

2. The development of increased information useful in the control of biological hazards of radiation, either through minimization of exposure or protection against biological effects.

3. Exploitation of nuclear radiations and of radioactive materials in studies of basic biological processes.

4. Improving and developing techniques for the use of radiations in medical diagnosis and therapy.

The research was carried out largely at the Commission's government-owned contractor-operated (GOCO) laboratories and facilities and by contract with universities, hospitals and other institutions. Research conducted at the GOCO facilities was technically monitored by the AEC staff in Washington, D. C. The various contractors submitted scientific proposals for research to AEC and, if approved and funded, the work was conducted by the proposing contractor. The contracts were management-type contracts whereby the AEC staff technically monitored the performance of approved work but was not involved in supervising the work which was carried out by contractor employees.

Shortly after the AEC was created in 1947, the Advisory Committee on Biology and Medicine was formed by the Commission to advise them on organizing the Division of Biology and Medicine. The Advisory Committee subsequently reviewed periodically the biomedical program of AEC and reported to the Commission on the quality of these research projects. As the new Division's initial major program, the Advisory Committee recommended establishing at each national laboratory a clinical research facility to take advantage of the unique radioactive material in diagnosis and treating cancer. The primary facility was to be the Argonne Cancer Research Hospital as an adjunct to the School of Medicine of the University of Chicago, with smaller hospitals at Oak Ridge and Brookhaven National Laboratories. Early in 1948, the AEC moved to implement the Committee's recommendation.

The AEC already had a contract with the Oak Ridge Institute of Nuclear Studies (ORINS), a nonprofit, educational corporation whose membership was composed of universities and colleges in the Southern Region*. Under the existing contract, ORINS was training scientific personnel from institutions throughout the country in the use of radioisotopes and was arranging for graduate students and university faculty members to come to Oak Ridge to participate in research programs. In addition, ORINS was also conducting a program whereby young scientists employed in Oak Ridge could work toward their masters' and doctors' degrees without leaving their positions to return to school.

*ORINS Member Institutions - 1948

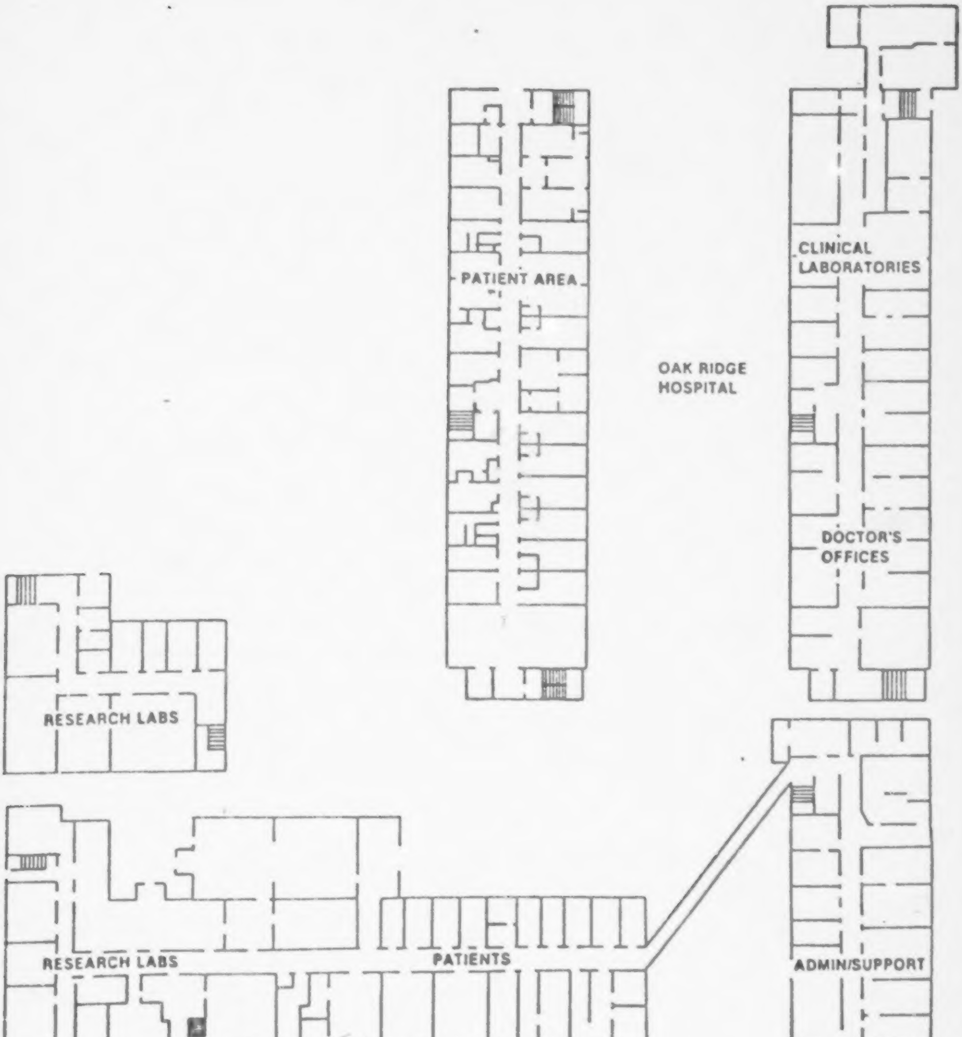
University of Alabama
University of Arkansas
Auburn University
Catholic University of America
Duke University
Emory University
University of Florida
University of Georgia
Georgia Institute of Technology
University of Kentucky
Louisiana State University
University of Mississippi
University of North Carolina
University of Tennessee
University of Texas at Austin
Tulane University
Vanderbilt University
University of Virginia

In February 1948, the Division of Biology and Medicine asked ORINS to consider the feasibility of establishing and operating an Oak Ridge clinical research facility. In March 1948, ORINS convened a meeting of the representatives of each Southern Medical School to determine the feasibility of establishing such a clinical research facility in Oak Ridge for the study of neoplastic diseases using the exceptional research tools available there. At the end of the conference, a recommendation was made to AEC that ORINS proceed with the proposed clinical facility to be housed in an unused wing of the AEC-owned and contract-operated community hospital. Following approval of the ORINS proposed operating plan by AEC, construction of a laboratory building and renovation of the adjacent existing hospital wing was begun. ORINS appointed Dr. Marshall H. Brucer as Chairman of the Medical Division. In early 1950, the first patient was admitted to the Medical Division. The floor plan of the original clinical facility operated by ORINS is shown in Figure 1. For reference purposes, the location of the AEC community hospital is also shown.

During the early fifties, the ORINS Medical Division developed methods of synthesizing radiolabelled compounds and preparing them for clinical trials. Early attempts at radioisotope therapy were largely unsuccessful. At the same time that internally administered therapeutic radioisotopes were being studied, ORINS was also conducting an active program to develop external radioisotope sources to be used in place of x-rays to produce an

Figure 1

FACILITIES 1940's—60's


PATIENT AREA
CLINICAL LABORATORIES
OAK RIDGE HOSPITAL
DOCTOR'S OFFICES
RESEARCH LABS
RESEARCH LABS
PATIENTS
ADMIN/SUPPORT
ORINS

external beam that could be directed into the body as a treatment of cancer. By late 1951, an efficient cobalt-60 teletherapy machine had been designed and placed in a specially built room at ORINS. After testing, it was moved to M. D. Anderson Hospital in Houston for clinical trials. Early in 1952, the ORINS Medical Division began a teletherapy evaluation program to determine which of several potentially useful radioisotopes would prove most useful in teletherapy. Cobalt-60 became the most widely used teletherapy source and before long this form of therapy was common all over the world.

During this period, radioiodine-131 had become available from Oak Ridge National Laboratory and as a result numerous clinics throughout the United States were using it for the diagnosis and treatment of thyroid cancer. Unfortunately, there was no uniformity in methods used to measure the administered dose or the amount of radioisotope localized in the thyroid gland. In 1954, ORINS initiated a radioiodine uptake calibration program. Several fashion store mannequins were purchased and artificial thyroid glands with accurately known levels of mock iodine were placed in their necks. These calibration kits were sent from one laboratory to another around the country where each clinician used his own instruments to measure the thyroid dose and uptake of the mannequin. All results were reported to the Medical Division where they were compared with expected values. As anticipated, there were wide discrepancies from the standard in the results obtained. Through collaboration between Oak Ridge National Laboratory and ORINS a new instrument was designed which soon became widely available commercially and made radioiodine thyroid diagnosis and treatment a reliable and standard clinical procedure.

The Medical Division also devoted a major effort to human total body irradiation studies to improve the treatment for certain types of leukemia and lymphoma. Prior to 1960, the total body irradiation was given to the patients using a colbalt-60 teletherapy unit.

In June 1958, eight workers at the AEC Y-12 plant in Oak Ridge were involved in a radiation accident. Their doses ranged from 23 to 365 rads, with five of the men receiving more than 225 rads. All of the men were treated at the ORINS Medical Division and subsequently recovered uneventfully.

As a result of the Y-12 accident, it became clear that more information on the response of the human to radiation was needed. The film badges worn by the workers were unreliable indicators of actual exposure and a biological measure of exposure was needed to aid the clinician in handling such cases.

Dr. Gould Andrews who began his career at ORINS in 1949 as Chief of Hematology developed a special interest in the hematologic effects of radiation and studied the Y-12 men over the next 21 years. He also developed an acute interest in the hematologic response of patients exposed to total-body irradiation therapeutically to better learn how to predict and treat these effects in exposed workers. As a result of this knowledge, Dr. Andrews was usually called to consult at other institutions where accidents had occurred. The ORINS Medical Division was the designated hospital for handling any radiation accident at the AEC plants in Oak Ridge. In order to provide the best possible care in case of an accident the AEC expected that hematologic data from patients being treated with total body irradiation in addition to being used to benefit other patients would also be used to benefit any radiation accident victim.

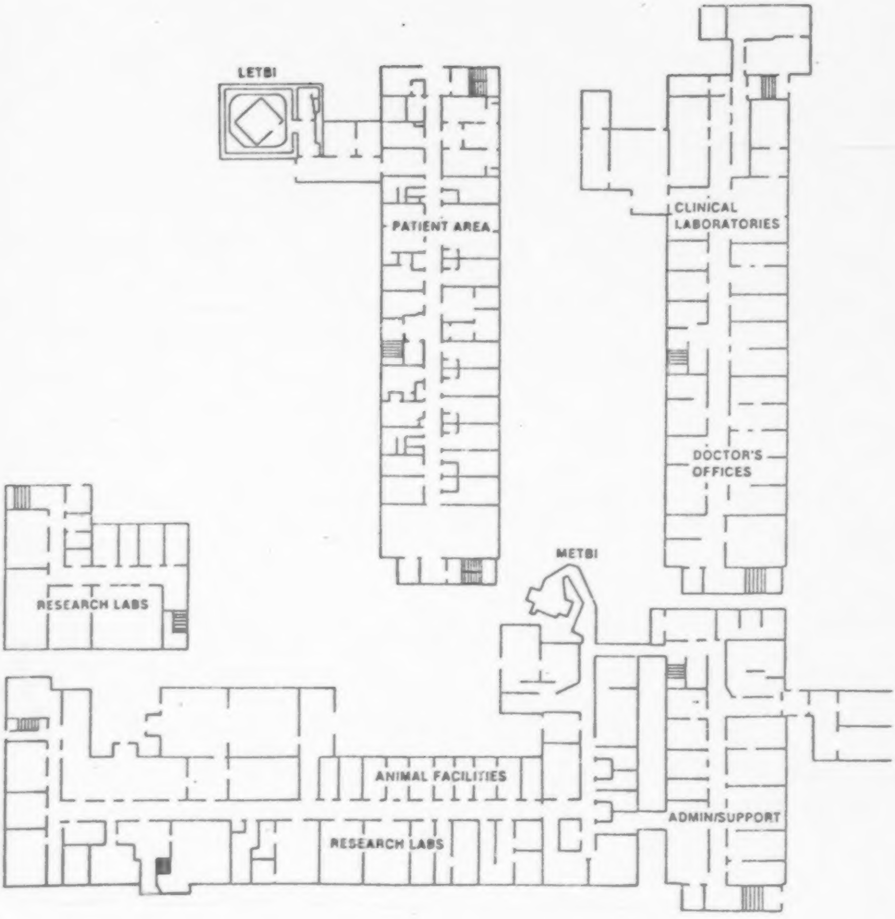
In 1960, the new Oak Ridge hospital was completed and the patients moved out of the AEC community hospital. The old hospital was renovated and the ORINS Medical Division patients moved into this facility.

The teletherapy machines available in the late 1950's did not give uniform radiation fields such as one would prefer for total body radiation therapy. During irradiation treatment using teletherapy, the patient had to be moved to try and provide for a fairly uniform exposure. To solve this problem, ORINS designed and constructed a new facility which was a concrete shielded room containing eight radiation sources and delivered a uniform dose to the patient. This facility, called Medium Exposure Total Body Irradiator (METBI), was completed in 1959 and began operation in 1960. In the METBI facility, patients would lay on a bed located in the center of the room during radiotherapy. Radiation sources were operated remotely and the patient was monitored visually by specially arranged mirrors at the control panel in an adjacent room. The patient was able to communicate with the technician during treatment by means of an intercom system.

Figure 2 is a schematic of the ORINS Medical Division in 1968 showing this renovation and includes the whole-body counter and METBI and LETBI facilities.

In 1960, an immunology program was started at ORINS to study the effects of radiation on immune responses and the immunology of bone morrow transplantation. In order to study the types of infections that occur in patients with bone marrow damage from radiation and chemotherapy, a research program in microbiology was also initiated in 1960.

FACILITIES IN 1965


LETBI
PATIENT AREA
CLINICAL LABORATORIES
DOCTOR'S OFFICES
RESEARCH LABS
METBI
ANIMAL FACILITIES
ADMIN/SUPPORT
RESEARCH LABS

In late 1961, Dr. Brucer retired as Chairman of the ORINS Medical Division and the following year Dr. Gould Andrews was appointed as his successor.

AEC was the Federal Agency responsible for developing the basic biological knowledge for use by other organizations and institutions in developing radiation protection standards. Thus, it was normal for the National Aeronautics and Space Administration to approach AEC in 1963 for assistance in determining biological risks astronauts might encounter during space travel. Such data were needed by NASA in order to determine the amount of shielding required to protect the astronauts. It was agreed that AEC would be responsible for collecting radiobiological information from hospital records of patients who had received therapeutic whole-body irradiation and for analyzing the data for NASA. In return, NASA would reimburse AEC for costs incurred in conducting the study. Under the existing AEC-NASA interagency agreement, the project was assigned to ORINS Medical Division by AEC. Following a feasibility study in which medical records at ORINS were examined to determine if useful data could be obtained from patients' charts, the ORINS study was expanded to 45 hospitals and eventually included radiobiologic information from over 2,500 therapeutic exposures. The results of this initial study were made available to the National Academy of Sciences and were published in 1967 in "Radiobiological Factors in Manned Spaceflight".

As a result of animal studies on repair mechanisms, it was becoming obvious that radiation delivered at a slower rate had the potential for providing the same therapeutic benefit to the patient without causing the undesirable side effects observed at faster delivery rates. However, to get the same dose, the patient would need to be exposed for much longer periods of time. Such a facility to be known as the Low Exposure Total Body Irradiator (LETBI) to test this idea in a clinical environment was proposed by ORINS to AEC in 1965.

At the time LETBI was first proposed to AEC, ORINS suggested that in addition to the clinical studies for AEC, subsequent analysis of the stored data might be of value to NASA. For the AEC, LETBI was intended to provide information on the possible benefit of low-dose rate total body irradiation as opposed to the move conventional higher dose rate facilities. The construction of LETBI was funded by AEC to provide this information in a one-of-a-kind facility. Should LETBI prove more beneficial than conventional methods, this concept would have been expected to be picked up by other clinical centers using whole body irradiation for cancer therapy. Since LETBI did not prove to be more beneficial than conventional means, only one such facility was constructed by AEC.

The Low Exposure Total Body Irradiation (LETBI) facility provided a comfortably furnished inner room 16 feet square in which there was an almost uniform radiation field. The radiation sources were positioned in a larger, outer, heavily shielded room.

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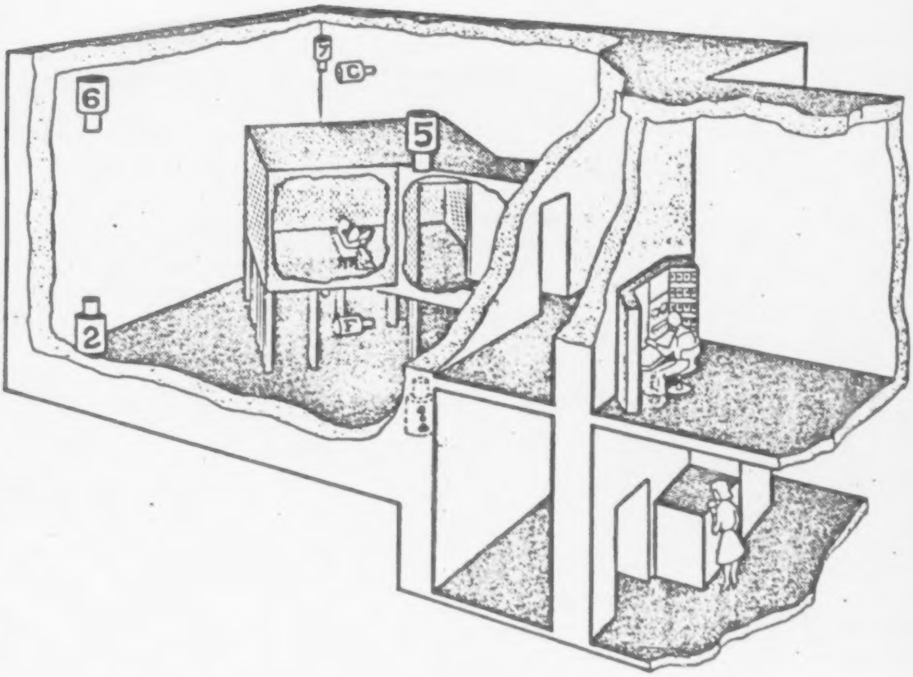
A diagram of the LETBI facility is shown in Figure 3.

With the completion of the Low Exposure Total Body Irradiator (LETBI) in 1967, it became possible to collect continuous patient monitoring data during long exposure periods to low dose rate radiation. Although the elaborate physiological monitoring was designed to monitor the patient continuously during treatment, it was also possible to simultaneously preserve the same data on tape for subsequent analysis.



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The storage and analysis of patient data collected as part of the AEC funded LETBI program was beyond the scope of the AEC program and all AEC costs for this activity were reimbursed by NASA. It should be emphasized that all activities related to the clinical treatments using the LETBI facility were funded by AEC.

In January 1966, ORINS underwent a name change to the current Oak Ridge Associated Universities.

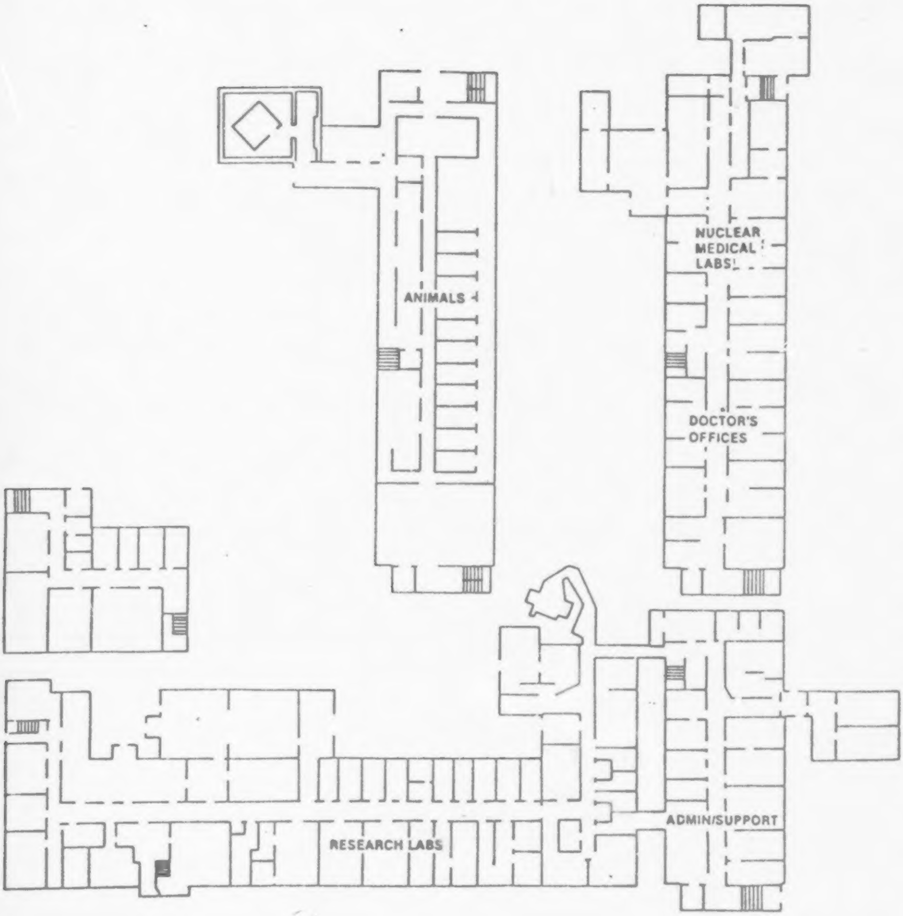
By the early 1970's, it was becoming clear that while the treatment of patients at the ORAU Medical Division was excellent, the number of cases treated was too small to be statistically significant in evaluating various modalities of therapy. Moreover, since all costs related to patient care were borne by AEC, it was becoming increasingly difficult to justify the continued operation of this, and other, AEC hospitals. Whereas in the early fifties and sixties, these AEC hospitals were responsible for developing the whole new field of nuclear medicine by the late sixties, their influence had spread and nuclear medicine was well advanced at most major medical centers. Physicians who had been trained at these AEC hospitals had returned to their universities and were now conducting the training. The AEC hospitals had in effect put themselves out of business.

The ORAU clinical cancer research program was terminated in 1974 with the closing by AEC of the inpatient care facility. In 1975, Dr. C. C. Lushbaugh became the Chairman of the newly named ORAU Medical and Health Sciences Division. Following the closing of the clinical inpatient facility, the building was again renovated and its current configuration is shown in Figure 4.

When the decision was made to close the hospital, all patients who participated in the cancer treatment program were offered the option for continued treatment by private physicians in Oak Ridge or hospitalization in the Oak Ridge Hospital of the United Methodist Church. In the former, AEC would reimburse any difference in costs between their insurance and the doctor's fees. In the latter, AEC would pay any charges over and above those the patients' insurance would pay. DOE continues to pay some of the costs for care of the former patients.

The third floor which formerly housed patients was converted to a modern animal care facility to support the ongoing basic research and radiopharmaceutical development programs.

PRESENT FACILITIES


NUCLEAR MEDICAL LABS
ANIMALS
DOCTOR'S OFFICES
ADMIN/SUPPORT
RESEARCH LABS

ORAU is continuing its long standing program in the development of radioactive labeled compounds for the diagnosis of disease. With joint funding from the National Cancer Institute and DOE, ORAU is using a special device designed for what is known as Emission Computerized Axial Tomograhy (ECAT) in out-patient clinical trials.

Mr. Chairman, this concludes my statement. I would be pleased to answer any questions.

Mr. GORE. OK. Thank you. Thank you for enclosing the graphic description of the facilities, which makes it easier to understand for those reading this testimony.

Now Dr. William Burr, I take it you have a short prepared statement.

Dr. BURR. Yes, sir, I have a very short statement that I will read.

Mr. GORE. Go ahead.

Dr. BURR. Mr. Chairman, I appreciate the opportunity to attend this hearing.

Several months ago I retired from Federal service after a number of years first with the Atomic Energy Commission, and then the Energy Research and Development Administration, and finally with the Department of Energy, where I most recently served as the Deputy Assistant Secretary for Environmental Research, and prior to that as the Director of the Office of Health and Environmental Research.

From 1961 to 1969 I was Chief of the Medical Research Branch in the Division of Biology and Medicine of the Atomic Energy Commission. This branch had the primary responsibility within the Division of Biology and Medicine for the technical monitoring of programs at the Medical Division at the Oak Ridge Associated Universities. The role of the branch staff was to review and evaluate proposals for programs and to make recommendations to the Director of the Division of Biology and Medicine regarding support for new work or, in the case of ongoing progams, to recommend as to the continuation of the work. In reviewing programs, staff from other branches of the division might also be involved, as well as experts from the scientific community.

Actual proposals for the support were developed in the various laboratories and, if approved by the Division of Biology and Medicine, technical direction and conduct of the work resided with the laboratory. The laboratories in turn had their own review processes established by their directors to consider their work independently.

Dr. Edington has very adequately described the purpose of the programs and the procedures followed by the Division of Biology and Medicine in monitoring the progress of research.

Dr. Bibb has prepared an extensive chronological description of the work conducted at ORINS and subsequently at ORAU, and I feel there is very little that I can specifically add from my own recollection.

I would like to emphasize, as Dr. Edington and Dr. Bibb have pointed out, that the research in the Division of Biology and Medicine had multiple objectives, one of these being the effort to develop beneficial applications of radiation and radionuclides. The work of the Medical Division at Oak Ridge Associated Universities was primarily focused on this objective, and over the years this group has made many contributions both to diagnostic and therapeutic medical applications of radiation and radionuclides. The ORAU medical program played a particularly important role in the early years following its establishment, not only in the development of new methodologies and in the standardization of procedures to be used in medicine, but also in the transfer of new knowledge to the medical community through the training of university scientists and physicians.

Mr. Chairman, I will be pleased to assist in answering any questions to which I can contribute.

Mr. GORE. Thank you very much.

Our final witness on this panel is Andrew J. Stofan, Acting Associate Admnistrator for Office of Space Science at NASA.

Have I pronounced your name correctly?

Mr. STOFAN. Yes, sir.

Mr. GORE. Welcome, and please proceed.

Mr. STOFAN. Thank you.

Mr. Chairman and members of the subcommittee, I appreciate the opportunity to report to the subcommittee the facts, to the best of my knowledge, relating to NASA's role in the radiobiological studies carried out by AEC during the years 1964 to 1974 at the Medical Division of Oak Ridge Associated Universities (ORAU), formerly called Oak Ridge Institute of Nuclear Studies (ORINS). Our records of some of the early studies initiated by NASA Headquarters, such as the one with ORINS/ORAU, are incomplete. The NASA file covering this period is not available, because it was retired and later destroyed in accordance with prescribed practice. Some NASA personnel associated with this ORINS/ORAU project have since retired, returned to their parent organizations, or are currently employed elsewhere. However, the available technical monitors and others closely associated with the project have been queried and have supplied their best recollection of key events.

Because NASA is responsible for the health and safety of astronauts, NASA has been interested in characterizing the natural radiation environment of space. This radiation consists of two main types: relatively constant, low-dose-rate electron and proton radiation from the geomagnetically trapped Van Allen Belts and sporadic, high-dose-rate solar particle vents. NASA has had a special interest in the radiobiological responses of man, such as nausea, vomiting and fatiguability, as directly related to his ability to function efficiently in space.

To assist NASA in assessing these radiation problems, the Space Science Board of the National Academy of Sciences convened working groups in 1961 and again in 1964. The membership of the latter panel, consisting of distinguished scientists in the field of radiation biology at the time, is given in appendix A of my statement. In its report, "Radiobiological Factors in Manned Space Flight," the panel reviewed and extended some of the more pertinent information on radiobiology with emphasis on human responses to the potential radiation risks accompanying space flights. This report formed the foundation for NASA's efforts with respect to safeguarding man in the potentially lethal radiation environment of space. The radiation dose-response tables and curves presently used in mission control for Shuttle flights are largely based on this report. These data enable flight controllers to predict the likely response of astronauts to high levels of radiation, for example, solar flares.

The panel's report summarized what was known at that time concerning the dose responses of man to radiation and it outlined the data needed to derive more precise and definitive evaluations of risks.

In its recommendations the panel noted that, and I quote:

> There is presently and always will be an obvious need for more human data, particularly with regard to radiation dose-response relationships and effects of various modifying factors thereon.

It also noted that:

> The rate of accumulation of such data is slow and advantage should be taken of every ethical means to obtain more information collected under conditions that permit better risk evaluations . . .

The report further states:

> Wherever possible, opportunities to improve the quality of human data should be sought out and encouraged.

Based on these recommendations and on NASA's operational need for more precise data concerning the effects of radiation on living systems, an effort was initiated in the early 1960's to accumulate data from ongoing radiobiological treatment programs being carried out by other organizations. Although, as I have indicated, the record is incomplete, we have been able to establish the following chronology:

During the early sixties, coincident with the deliberations of the space radiation study panels, NASA became aware of ongoing clinical research effort by AEC to investigate the potential of ionizing radiation in the treatment of neoplastic disease (cancer). These AEC studies had been initiated as early as 1957.

In December 1963, AEC proposed to NASA that a research project entitled, "Retrospective Study of Radiation Effects" be conducted at ORINS. The objective of this retrospective, or "backward-looking," project was to establish the radiosensitivity of man by analyzing past medical records gained from accidental and therapeutic radiation exposures. NASA accepted the proposal.

In substance, the ORINS investigators were to examine the medical records of a large number of persons throughout the country who had been treated in the past with various regimens of radiation. The long-range goal of this initial retrospective project was to establish the radiosensitivity of man based on human experience gained from accidental and principally therapeutic radiation exposures. Ultimately, approximately 3,000 cases of human therapeutic exposure experiences from 45 contributing institutions were combined with approximately 100 case experiences accumulated at the ORINS/ORAU Medical Division to establish this data base.

During the same early period, AEC, ORINS, and NASA personnel held discussions concerning a prospective study of human radiobiological responses to low dose-rate radiation. In a prospective study, investigators know ahead of time the types of information they are seeking, therefore they can avoid the information gaps that invariably exist in some of the medical histories employed in retrospective studies. The opportunity to conduct a prospective data collection program of human responses to low-dose-rate irradiation arose because ORINS was planning to examine the therapeutic value of such irradiations.

In this early time period, discussions about the new prospective program were held between AEC, ORINS, and NASA. It was determined that NASA has an interest in the data that could be derived from the clinical therapy in the low-exposure-rate total body irradiation (LETBI) and it was agreed that NASA would make a contribution to the facility. Subsequently, the AEC assumed the cost for the actual design and construction of the facility and NASA assumed the cost for the equipment, principally biomedical instrumentation for physiological monitoring, and radiation sources. Total equipment cost was estimated at $65,000. It is NASA's understanding that LETBI would have been constructed and used without NASA funding.

The biomedical instrumentation, developed by AEC/ORINS, was to allow the monitoring of the patients' well-being and vital signs during radiation therapy. For example, the bioinstrumentation would allow monitoring of electrocardiogram, heart rate, respiration rate, respiration waveform, and temperature from start of irradiation. This constant monitoring would obviate the need to disrupt the radiation treatment to acquire this information by manual means. Some of these data, the respiration waveform data, would also serve to indicate incipient nausea, of particular interest to NASA.

It should be reemphasized that NASA's interest in this prospective study was solely in acquiring accurate radiation dose-response data on a noninterference basis from the AEC/ORINS clinical study of the effectiveness of low-level total body radiation in treating persons with certain types of neoplastic diseases—lymphoma, leukemia. I have found no evidence that NASA had any role in the selection of patients, selection of therapeutic modality, referral of patients, or any other aspect of the clinical study. NASA was interested only in acquiring data from adult human radiation exposure.

During its inception in mid-1964 up until 1969 this project was funded by NASA Headquarters. In late 1969, technical monitorship of the effort was transferred from NASA Headquarters to the Manned Spacecraft Center at Houston, where it remained until the effort was terminated June 30, 1975.

NASA understands the total funding of the program, including NASA's $2.2 million, was on the order of $26 million.

In summary, Mr. Chairman, I would like to provide answers, based on our review of this matter, to the questions you raised in your letter requesting NASA testimony on this subject. You asked what agency proposed the initial study and what agency proposed construction of the LETBI facility. It was the Atomic Energy Commission which submitted a formal proposal to NASA after preliminary discussions between technical personnel of both agencies had taken place in late 1963. In the 1963-64 time period, it is our understanding that ORINS proposed to AEC the construction of the LETBI.

You requested a description of the relationship and interaction between NASA and the ORAU, formerly ORINS, Medical Division. NASA transferred funds to the AEC, which, in turn, awarded a contract to ORINS for the analysis of data resulting from therapeutic and accidental radiation exposure. Written reports of the results of these analyses were submitted to NASA.

You asked whether NASA had any input concerning selection of patients. NASA had no role in the selection of any patient.

You asked about NASA input on the treatment of patients. Again, NASA had no role in the treatment of any patient.

And, Mr. Chairman, you asked whether the total body irradiation doses given to patients were changed as a result of the NASA study. NASA did not influence the choice of the radiation dose administered to any patient. We were simply seeking data on the response to treatment provided to patients by ORINS.

You also asked what steps NASA took to insure that patients were fully informed. The responsibility for insuring that patients were informed of and consented to the total body irradiation therapy rested solely with the institution providing medical treatment. NASA assumed no role in this regard, since NASA was not involved in the treatment. NASA was seeking data that resulted from treatment.

That concludes my testimony, Mr. Chairman and members of the subcommittee.

[The prepared statement, plus answers to questions asked of Mr. Stofan, follow:]

Mr. GORE. Thank you very much.

Statement of

Andrew J. Stofan
Acting Associate Administrator for
Office of Space Science

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

before the

Subcommittee on Investigations and Oversight
Committee on Science and Technology
U.S. House of Representatives

Mr. Chairman and Members of the Subcommittee:

I appreciate the opportunity to report to the Subcommittee the facts, to the best of my knowledge, relating to NASA's role in the radiobiological studies carried out by AEC during the years 1964 to 1974 at the Medical Division of Oak Ridge Associated Universities (ORAU), formerly called Oak Ridge Institue of Nuclear Studies (ORINS). Our records of some of the early studies initiated by NASA Headquarters, such as the one with ORINS/ORAU, are incomplete. The NASA file covering this period is not available, because it was retired and later destroyed in accordance with prescribed practice. Some NASA personnel associated with this ORINS/ORAU project have since retired, returned to their parent organizations or are currently employed elsewhere. However, the available technical monitors and others closely associated with the project have been queried and have supplied their best recollection of key events.

Because NASA is responsible for the health and safety of astronauts, NASA has been interested in characterizing the natural radiation environment of space. This radiation consists of two main types: relatively constant, low dose-rate electron and proton radiation from the geomagnetically trapped van Allen belts and sporadic, high dose-rate solar particle events. NASA has had a special interest in the radiobiological responses of man, such as nausea, vomiting and fatiguability, as directly related to his ability to function efficiently in space.

To assist NASA in assessing these radiation problems, the Space Science Board of the National Academy of Sciences convened working groups in 1961 and again in 1964. The membership of the latter panel, consisting of distinguished scientists in the field of radiation biology at the time, is given in Appendix A. In its report, Radiobiological Factors in Manned Space Flight, the panel reviewed and extended some of the more pertinent information on radiobiology with emphasis on human responses to the potential radiation risks accompanying space flights. This report formed the foundation for NASA's efforts with respect to safeguarding man in the potentially lethal radiation environment of space. The radiation dose-response tables and curves presently used in Mission Control for Shuttle flights are largely based on this report. These data enable flight controllers to predict the likely response of astronauts to high levels of radiation (e.g., solar flares).

The Panel's report summarized what was known at that time concerning the dose-responses of man to radiation and it outlined the data needed to derive more precise and definitive evaluations of risks.

In its recommendations the Panel noted that, "There is presently and always will be an obvious need for more human data, particularly with regard to radiation dose-response relationships and effects of various modifying factors thereon." It noted that, "The rate of accumulation of such data is slow and advantage should be taken of every ethical means to obtain more information collected under conditions that permit better risk evaluations..." The report further states, "Wherever possible, opportunities to improve the quality of human data should be sought out and encouraged."

Based on these recommendations and on NASA's operational need for more precise data concerning the effects of radiation on living systems, an effort was initiated in the early 1960's to accummulate data from ongoing radiobiological treatment programs being carried out by other organizations. Although as I have indicated the record is incomplete, we have been able to establish the following chronology:

During the early sixties, coincident with the deliberations of the Space Radiation Study Panels, NASA became aware of on-going clinical research efforts by AEC to investigate the potential of ionizing radiation in the treatment of neoplastic disease (cancer). These AEC studies had been initiated as early as 1957.

In December 1963, AEC proposed to NASA that a research project entitled, "Retrospective Study of Radiation Effects," be conducted at ORINS. The objective of this retrospective, or "backward-looking," project was to establish the radiosensitivity of man by analyzing past medical records gained from accidental and therapeutic radiation exposures. NASA accepted the proposal.

In substance, the ORINS investigators were to examine the medical records of a large number of persons throughout the country who had been treated in the past with various regimens of radiation. The long range goal of this initial retrospective project was to establish the radiosensitivity of man based on human experience gained from accidental and principally therapeutic radiation exposures. Ultimately 3,000 cases of human therapeutic exposure experiences from 45 contributing institutions were combined with 100 case experiences, accumulated at the ORINS/ORAU Medical Division to establish this data base.

During the same early period, AEC, ORINS and NASA personnel held discussions concerning a prospective study of human radiobiological responses to low dose-rate radiation. In a prospective study, investigators know ahead of time the types of information they are seeking, therefore they can avoid the information gaps that invariably exist in some of the medical histories employed in retrospective studies. The opportunity to conduct a prospective data collection program of human responses to low dose-rate irradiation arose because ORINS was planning to examine the therapeutic value of such irradiations.

In this early time period, discussions about the new prospective program were held between AEC, ORINS and NASA. It was determined that NASA had an interest in the data that could be derived from the clinical therapy in the Low Exposure-rate Total Body Irradiation (LETBI) and it was agreed that NASA would make a contribution to the facility. Subsequently, the AEC assumed the cost for the actual design and construction of the facility and NASA assumed the cost for the eqiupment (principally bioinstrumentation for physiological monitoring) and radiation sources. Total equipment cost was estimated at $65,000. It is NASA's understanding that LETBI would have been constructed and used without NASA funding.

The bioinstrumentation, developed by AEC/ORINS, was to allow the monitoring of the patients' well-being and vital signs during radiation therapy. For example, the bioinstrumentation would allow monitoring of electrocardiogram, heart rate, respiration rate, respiration waveform, and temperature from start of irradiation. This constant monitoring would obviate the need to disrupt the radiation treatment to acquire this information by manual means. Some of these data (the respiration waveform data) also would serve to indicate incipient nausea, of particular interest to NASA.

It should be reemphasized that NASA's interest in this prospective study was solely in acquiring accurate radiation dose-response data on a non-interference basis from the AEC/ORINS clinical study of the effectiveness of low-level total body radiation in treating persons with certain types of neo-plastic diseases (lymphoma, leukemia). I have found no evidence that NASA had any role in the selection of patients, selection of therapeutic modality, referral of patients, or any other aspect of the clinical study. NASA was interested only in acquiring data from adult human radiation exposure.

During its inception in mid-1964 up until 1969 this project was funded by NASA Headquarters. In late 1969, technical monitorship of the effort was transferred from NASA Headquarters to the Manned Spacecraft Center at Houston, where it remained until the effort was terminated June 30, 1975.

NASA understands the total funding of the program, including NASA's $2.2 million, was on the order of $26 million.

In summary, Mr. Chairman, I would like to provide answers, based on our review of this matter, to the questions you raised in your letter requesting NASA testimony on this subject. You asked what agency proposed the initial study and what agency proposed construction of the LETBI facility. It was the Atomic Energy Commission which submitted a formal proposal to NASA after preliminary discussions between technical personnel of both agencies had taken place in late 1963. In the 1963-64 time period, it is our understanding that ORINS proposed to AEC the construction of the LETBI.

You requested a description of the relationship and interaction between NASA and the ORAU (formerly ORINS) Medical Division. NASA transferred funds to the AEC which in turn awarded a contract to ORINS for the analysis of data resulting from therapeutic and accidental radiation exposure. Written reports of the results of these analyses were submitted to NASA.

You asked whether NASA had input concerning selection of patients. NASA had no role in the selection of any patient.

You asked about NASA input on the treatment of patients. NASA had no role in the treatment of any patient.

And, Mr. Chairman you asked whether the total body irradiation doses given to patients were changed as a result of the NASA study. NASA did not influence the choice of the radiation dose administered to any patient. We were simply seeking data on the response to treatment provided to patients by ORINS.

You also asked what steps NASA took to insure that patients were fully informed. The responsibility for insuring that patients were informed of and consented to the total body irradiation therapy rested solely with the institution providing medical treatment. NASA assumed no role in this regard, since NASA was not involved in the treatment. NASA was seeking data that resulted from treatment.

That concludes my testimony, Mr. Chairman and Members of the Subcommittee.

Appendix A

1964
Space Radiation Study Participants

Panel

Chairman - Wright H. Langham, Los Alamos Scientific Laboratory, University of California, Los Alamos, New Mexico

Co-Chairman - Douglas Grahn, Argonne National Laboratory, Argonne, Illinois

Victor P. Bond, Brookhaven National Laboratory, Upton, Long Island, New York

Robert A. Conard, Brookhaven National Laboratory, Upton, Long Island, New York

Howard J. Curtis, Brookhaven National Laboratory, Upton, Long Island, New York

Samuel P. Hicks, University of Michigan, Ann Arbor, Michigan

C. C. Lushbaugh, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee

G. M. McDonnell, University of California, Los Angeles, California

James J. Nickson, Michael Reese Hospital, Chicago, Illinois

Hermann J. Schaefer, U.S. Naval Aerospace Medical Institute, Pensacola, Florida

Charles A. Sondhaus, University of California, College of Medicine, Los Angeles, California

Herman D. Suit, M. D. Anderson Hospital and Tumor Institute, University of Texas, Houston, Texas

Consultants

Gould A. Andrews, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee

Gilbert H. Fletcher, M. D. Anderson Hospital and Tumor Institute, University of Texas, Houston, Texas

Elizabeth F. Focht, New York Hospital-Cornell Medical Center, New York City, New York

Carl G. Heller, Pacific Northwest Research Foundation, Seattle, Washington

George R. Merriam, Jr., Institute of Ophthalology, New York City, New York

John F. Thomson, Argonne National Laboratory, Argonne, Illinois

Paul C. Tompkins, Federal Radiation Council, Washington, DC

Shields Warren, New England Deaconess Hospital, Boston, Massachusetts

Responses to written questions submitted by Chairman Gore during the hearing before the House Subcommittee on Investigations and Oversight on September 23, 1981.

Question 1:

What is the NASA procedure for retiring and destroying records?

Answer 1:

NASA procedures for retiring and destroying records comply with the provisions of 44 U.S.C. § 2901-2902, 3101-3106, 3301-3311 and the GSA Records Management Regulations issued implementing the statute found in 41 CFR 101-11. Specific direction to NASA organizations are given through the provision of the NASA Record Disposition Handbook (NHB 1441.1A) by the NASA Records Management Officer. The NASA Records Control Schedules found in NHB 1441.1A are mandatory and provide for (1) the preservation of records which are of long term or permanent value; (2) the prompt disposal of records which do not warrant further retention; and (3) the transfer of records to NASA installation staging areas and to Federal Records Centers which are no longer needed on current business but are not eligible for immediate disposal.

Question 2:

When were the records covering the NASA/AEC 1964-1974 study on the Radiosensitivity of Man retired and destroyed?

Answer 2:

According to our records, NASA Headquarters Grant No. R-0104-09 with the Atomic Energy Commission for subject work was completed in 1968, administratively closed-out on May 5, 1974, subsequently retired and transferred to the Federal Records Center, and destroyed on May 31, 1980.

To our best knowledge, there were no previous or subsequent contracts, grants, or other procurements issued out of our Division which dealt with this research area.

The disposition of these records was made in accordance with NHB 1441.1A, NASA Records Disposition Handbook, Item 1.a. (1)(b) of Schedule 17 (Procurement and Supply Records).

Question 3:

How long was Evelyn Repplinger employed by NASA and in what capacity?

Answer 3:

Ms. Evelyn Repplinger was employed by the NASA Manned Spacecraft Center (now JSC) on May 20, 1963, and resigned on July 1, 1964. Initially, she was employed in the capacity of an Aerospace Technologist (AST) in Bioradiation Studies. She was subsequently reclassified as a physicist.

Question 4:

What was the final disposition of her proposal to use prisoners in California for radiation studies?

Answer 4:

No record has been found of the existence of any formal written proposal to use prisoners in California for radiation studies, and, except for the reference contained in the memorandum of Dr. Gould Andrews to Dr. Kniseley, Mr. Harmon, Dr. Parker and Dr. Pollard of December 20, 1963, no evidence has been located of any consideration being given by NASA to such a proposal. Furthermore, since no record has been found of NASA's sponsorship of any radiation studies on prisoners in California or elsewhere, it is assumed that Ms. Repplinger's suggestion was not given serious consideration.

Question 5:

Have there ever been any NASA-sponsored experimental studies using prisoners in California or any other state? If so, what was the nature of the study and when and where did it occur?

Answer 5:

Such studies have been sponsored by NASA on several occasions. In the early sixties, nutritional studies were conducted on prisoners who volunteered to be fed diets with protein replaced by mixtures of synthetic amino acids. Between about 1970 and 1973, prisoners were subjected to bedrest for two to eight weeks at USPHS Hospital in San Francisco. The prisoners were obtained from either Lompoc or the Federal Correction Institute in Safford, Arizona. NASA's interest was in the effects of bedrest on the musculoskeletal and circulatory systems.

As a preliminary matter, is it typical for NASA to destroy documents concerning a program critically reviewed by another agency after a set number of years?

Mr. STOFAN. Yes; I would say that is common practice. After a given number of years storage, they are reviewed and, if there is not a need known for them, then they are destroyed.

Mr. GORE. You have an established procedure?

Mr. STOFAN. To the best of my knowledge, yes; there is established procedure.

Mr. GORE. Can you provide us with a copy of that procedure? How many years before documents are destroyed?

Mr. STOFAN. I can provide the procedures under which NASA's documents are controlled.

[EDITOR'S NOTE.—Information requested is provided in response to Chairman Gore's written question.]

Mr. GORE. Do you know how many years is the standard procedure to wait before destroying documents?

Mr. STOFAN. No, I don't.

Mr. GORE. Well, we have been able to obtain copies of many documents relating to the relationship between NASA and AEC from the Department of Energy files, and I wish to at this point thank the Department of Energy for the cooperation that they have given us in locating the files and in letting us have full access, which of course we are entitled to in any event. But we have had some difficulty getting all of the documents that we wanted to from NASA and that is why I want to get this copy of the procedure. I do want to point out, however, that NASA has cooperated fully with members of my staff and have made repeated efforts to locate pertinent documents.

Is it your position that NASA or any other Government agency that contracts with others to embark upon, or to conduct human experimentation, has no responsibility to insure that the subjects of the experimentation offer informed consent or are treated according to appropriate protocols?

Mr. STOFAN. I can only speak for NASA because I do not know about the rest of the Government organizations. When we deal with another Government organization, we do not double monitor that organization, which again in turn monitors a contractor or a university. It is not NASA's practice; we don't do it now and didn't do it at the time.

Mr. GORE. Do you think you should?

Mr. STOFAN. No; I do not think we should. I don't think that having one Government agency monitor another Government agency who is monitoring a contractor is a good way to expend funds.

Mr. GORE. Well, it may be that at the conclusion of the inquiry—I do not want to do this prematurely, but maybe we will recommend that any Government agency contracting out experiments that involve human subjects ought to be required to make inquiries to satisfy themselves that the human subjects are being treated in an appropriate manner.

Now, I would like to put into the record at this point a memorandum dated January 3, 1964. I am sorry, I do not have copies of this for you, but it is to Dr. Knisely, Mr. Harmon, Dr. Parker, and Dr. Pollard, signed by Gould Andrews.

Now, Dr. Bibb, Gould Andrews was the head of the Medical Division at Oak Ridge at that time?

Dr. BIBB. Yes, sir.

[The memorandum mentioned above follows:]

FORM P-4

MEMORANDUM

TO Dr. Kniseley, Mr. Harmon, Dr. Parker, Dr. Pollard ✓ DATE December 20, 1963

SUBJECT

COPIES TO

I was met at the National Airport in Washington at 11:00 yesterday by Dr. Burr and Dr. Barr from the Division of Biology and Medicine. We went to lunch and talked at some length about the NASA project. They feel that ORINS should do the major work for NASA but they mentioned that since previously talking with us they have brought Dr. Doug Grahn of the Argonne National Laboratories into the picture as sort of a special consultant and liaison man. He is actually a geneticist by trade, but is very knowledgeable in physics and in operational matters relating to space flight. He has been working with NASA for four or five years and is anxious to be of help in connection with the present needs. He does not anticipate doing any research, but would like to help interpret biological problems for NASA in terms of his knowledge of their operational needs.

Dr. Barr also pointed out that some changes are going on constantly in NASA organization. The Office of Manned Space Flight in Washington has had a change in status. It is now considered an advisory staff office and is no longer in the direct line of authority over the Manned Space Center Laboratories at Houston. That is, while the Houston group used to get their money directly from the Office of Manned Space Flight, they now get it through NASA headquarters.

We then went to the new NASA building in Washington where we met Dr. Sherm Vinograd. He is a youngish, middle-aged M.D. who used to be in practice somewhere in Wisconsin or Minnesota, and is now playing an important role in the medical aspects of the space program. He is a very reasonable and pleasant person to deal with and seems fairly well informed. Meeting with us were two of his assistants, Ed McLaughlin, who is, I believe, trained in psychology, and Jeff Lindsey who is something of a statistician. We had a constructive discussion about the needs of the space program. I outlined ORINS' experience in total body irradiation. The whole context of the discussion was on the assumption that we would do the program for them, and we were trying to iron out details of the relationship. Burr and Barr were strongly supporting of the Medical Division's competence in this field.

One major point of discussion was emphasized by Dr. Vinograd and this was that he feels that the people in NASA are inclined to ask us to give them judgements that are outside of our competence; for example, whether a man under certain circumstances should be allowed to receive 50 rads of radiation. He feels that the only thing that we can do is to tell them what biological results one might expect from a given dose and from that point on the decision is entirely up to them since they must take into account all sorts of other hazards in space flight and balance the radiation hazards against such things as the risks and liabilities of added shielding weight. This position seemed to be acceptable to the NASA people. I did get the feeling that they are worried in general about radiation and perhaps haven't thought very much about just how they are going to make decisions and balance the various types of risks.

A second major point that was discussed was the relationship between the Office of Manned Space Flight in Washington and the space center at Houston, Texas. We have been closely in contact with Miss Evalyn Repplinger of the space center at Houston, and she has come forth with rather specific ideas about the project that we might do, and it became clear that really two types of projects are being considered and administratively they are not identical in the eyes of NASA. First of all is the project to make a "continuing" retrospective study assessing radiation effects in the human being insofar as this is possible from either published data or from unpublished data that we might obtain access to. The Office of Manned Space Flight in Washington is anxious to support this project as is the Houston center, and the impression is that this project is to go forward under support of the Washington office (AEC prefers to deal with the Washington office since they feel that the contracts originated by relatively lower level people of the NASA hierarchy in Houston might have less stability). Vinograd emphasized, however, that he was not in a position to support any original research. What he is thinking of is a retrospective analysis of data, which could, however, as he sees it, be a continuing and expanding project. We talked in terms of a budget of $60,000 or $70,000 for this program for the rest of FY-64 and a figure of [illegible] 000 was vaguely mentioned for the subsequent year. I said that this figure for FY-65 might not be adequate but they made no particular point about it and we did not discuss this at length.

The other aspect of the problem is that we have been considering a study that would involve new research to be done, either in our own laboratories or to be developed at other laboratories and administered through us. This is a project which Vinograd cannot support from his office, but which can be supported through the center at Houston. However, the people I met [illegible] did not want to go into any detail about this since they are in no position to support it.

Thus it appears that there are two projects: (1) a retrospective study to be supported through Washington, and, possibly, (2) a new research study to be supported through the center at Houston.

On the basis of a recent telephone conversation I had with Evalyn Repplinger, I have the impression that she also has available some $70,000 to support the retrospective study, and it is my guess that this money is available separately in both places; however, we are not in the position to use more than $60,000 or $70,000 anyway, in the rest of this fiscal year. Apparently the situation now is that we should start immediately to make concrete plans for the retrospective study, and as time goes by, analyze the plans for the investigative study to be done for the group in Houston. Vinograd pointed out that in my letter indicating the amount of time that we might have available from our present staff we had given the impression that we would be doing research for his project, and he wanted to emphasize that all he could support was the data-analysis part of the study. He is quite willing to accept data retrieval of apparatus as a logical expense. We did not go into any detail about the specific costs, or how the money would be spent.

Our next step is to prepare a 189 and submit to Biology and Medicine of AEC indicating our plans for the retrospective study. Presumably they particularly want the plans for the rest of FY-64. We did not really discuss how much the 189 should cover about future years. I will have to work this out by telephone with Nat Barr.

In trying to discover what the space project requires of us, I found that they were rather flexible and quite reasonable but in a hurry for some type of help. Apparently they have a bunch of figures established by some committee which are written in terms of arbitrary limits; that is, no man should be allowed to receive more than 20 rads for the eye, or something of that sort.... but the present figures they are working with give no suggestion about what biological effects could be expected at different levels. They feel that they need a more extensive and flexible type of information, so that they can decide what risks could be taken, and what the results would be. In terms of deadline, they would like very much to have some additional information in less than 6 months, if possible, but they do not mean by this any given amount of data should be analyzed. Perhaps they would like information already available, simply applied to their particular problems. I made it clear that we could not do an exhaustive study of past radiation experience within 6 months, and they made it clear that they expect this retrospective analysis program to be continuing and run on for an indefinite period. They are willing to make available to us indications of their need, the types of radiation that they will be dealing with, etc.

Other points came up for some mention. One of these was the plan so enthusiastically discussed with me late in November by Evalyn Repplinger to use prisoners in a prison in California for radiation experiments. It seems that there is a Dr. Chen who has some special relationship to the governor of California and has a situation where prisoners could be used for all sorts of experiments. The implication was that the radiation experiments could be worked in without publicity as a part of some nutrition studies. I told Miss Repplinger that I was extremely skeptical about the whole idea; that I felt that giving low doses of radiation to normals would not prove anything of much value, and that giving large doses would be very doubtful from a medical, legal, and ethical standpoint. It seemed difficult to dampen her enthusiasm for this, however. I found in Washington that this project is also known to Vinograd and AEC. Dunham [illegible] said that he would have nothing to do with it, under any circumstances. I told Vinograd of my great reservations and the possible damage that could occur from publicity about ill conceived and unjustified experiments. This seemed to fit in with the views of Barr and [illegible] on this topic. Miss Repplinger had indicated that I might be asked to serve along with Wright Langham as a consultant for this project, but since I have so many reservations about it, perhaps she will seek someone else.

Another problem that came up for incidental discussion was the fact that Secretary of Defense McNamara has recently said that the project of maintaining orbiting manned space centers would be transferred from NASA to the Air Force. This was presumably as a consolation to Air Force since they had lost some recent project. People in NASA apparently are not fully informed about this, and don't feel that the last word has been said about the administration of this project. One of the main needs for radiation data is for the manned orbiting information centers.

After talking to Vinograd, Lindsey and McLaughlin, we went in to see Dr. Knauf who is the chief of this division. He is a very pleasant, somewhat older, man who was extremely gracious and pleasant. He discussed the daily crises of the space program, and the "flaps" that they have every time that they have a newspaper report involving hazards to astronauts. It seems that radiation is one of their main concerns in this regard. Dr. Knauf said that he intended to try to obtain a consultant for himself on radiation effects who would be quite independent of us or any contracted program. This consultant would simply help him deal with some of these publicity aspects and give him advice about the radiation problem.

It was also brought out that the work we would be doing would be of great interest to the other main Washington offices, which are parallel to the office of manned space flight. These are the Office of Advanced Research Technology and the Office of Space Sciences. Biology people in the Office of Advanced Research Technology are Konecci and V[illegible], and in the Office of Space Sciences the biology work would be under a man named Orr Reynolds and a man named Jenkins.

In general, the meetings in Washington were very cordial and constructive and indicated a major role [illegible] on the other hand it is also clear that NASA is a very complex organization and there are many uncertainities still in our relationship.

GAA

Gould A. Andrews

GAA:arb

Mr. **Gore**. This memorandum summarizes one of the very early discussions between the AEC and NASA with respect to this contract, and it refers to a telephone call from Nat Barr and a conversation with Bill Burr. It also refers to an Evelyn Repplinger. Was Evelyn Repplinger, with NASA, Dr. Barr?

Dr. **Barr**. Mr. Chairman, I guess I don't recognize whether she was an employee of NASA at the time or not. I recall the name but I don't remember whether she was an employee of NASA or a consultant. I am sorry, sir.

Mr. **Gore**. Mr. Stofan, is that name familiar to you?

Mr. **Stofan**. No; it is not.

Mr. **Gore**. What about Dr. Billingham, AEC?

Dr. **Barr**. No, Dr. John Billingham was an employee of NASA.

Mr. **Gore**. NASA, all right. It refers to a conversation with Evelyn Repplinger and Dr. Billingham. Miss Repplinger had seemed somewhat disturbed because she felt that she had to write a work statement having to do with the retrospective study to be supported out of NASA headquarters.

Now, the inference I am drawing is that Miss Repplinger was an employee of NASA.

It says in this memo on page 2, Dr. Andrews said:

> Thus it appears that there are two projects: (1) A retrospective study to be supported through Washington, and possibly (2) a new research study to be supported through the center at Houston.

Dr. Burr, or any of the other witnesses, were there in fact two parts to the contract with NASA, one part of the work to be the retrospective analysis and the second part to be a prospective study?

Dr. **Burr**. I think it would be more appropriate for Dr. Barr to address that, since he was the coordinator.

Mr. **Gore**. Dr. Barr.

Dr. **Barr**. Mr. Gore, I have not seen the memo that you are referring to. But with respect to your specific question, while there might have been discussion as to points of support for this study within NASA, it never appeared that way, that this support came from one part of NASA and was handled through their headquarters contracting.

Mr. **Gore**. Did it involve both a retrospective study and a prospective study?

Dr. **Barr**. Sir, during the morning, retrospective and prospective has been used in two senses, one with regard to epidemiological investigations and then, as is the case now, with respect to the acquisition of data from such experiments.

It was initially the understanding in the conduct of this work that the work would be retrospective, both at other institutions and at ORINS. Later on, it became obvious to all, I believe, that the definition of data that was particularly relevant prior to the acquisition or random acquisition of such data would be an extremely helpful process. That kind of prospective planning ahead, identification of what kind of data was needed in the course of therapy experiments gradually evolved during the operation of this project.

Mr. **Gore**. Now, when you say the definition of the kind of data needed, does that mean that upon the completion of the retrospective study, where Dr. Lushbaugh, went out and studied the results of several thousand experiments done at hospitals around the country, and crunched the data in a way that produced a voluminous amount of material on what the specific radiobiological effects of each particular dose of radiation would be.

It was found, at the conclusion of that retrospective study, that some information was lacking and some doses were not represented by enough data points to derive useful conclusions, and that those gaps needed to be filled. Are you saying that?

Dr. **BARR**. I am saying, sir, that the Space Science Board, who had been looking at this question, as well as Dr. Lushbaugh's investigation, had broadly identified many areas in which human data were lacking and that the National Aeronautics and Space Administration had identified areas in which they had particular needs. Both before the initiation of Dr. Lushbaugh's retrospective studies and after, there were areas which were of particular interest to NASA, in which it was hoped that one could glean information from radiation and accident experiments.

Mr. **GORE**. And the specific information involves specific ranges of exposures; is that right?

Dr. **BARR**. Yes; I would say NASA was not interested principally, as the Atomic Energy Commission was at the time, in long-term chronic radiation and effects arising from that. Nor were they interested in the impacts of massive doses of radiation. Generally, they were interested in the impacts of radiation delivered whole body at levels of some hundreds of rads.

Mr. **GORE**. Some hundreds of rads?

Dr. **BARR**. Yes.

Mr. **GORE**. Now, the difference between a retrospective analysis and a prospective analysis where a program has dual goals, one data acquisition and one treatment, the difference between retrospective and prospective is of some significance, because the chances that the two goals would come into conflict are greatly enhanced when the experiments are prospective in nature and not just a retrospective analysis. So this is of some significance.

Now, Mr. Stofan, if NASA is going to participate with the AEC in funding a prospective study to obtain information on a specific range of radiation doses where human beings are involved, shouldn't they have some responsibility to see that they are safeguarded?

Mr. **STOFAN**. NASA had nothing to do with the treatment protocols. It was interested only in the data that came out of it. Therefore, NASA did not have the responsibility for the detailed treatment that went on with the patients. The money was transferred to the AEC and then down to the ORINS. So, NASA did not have a responsibility in that area.

Mr. **GORE**. Dr. Barr, was the design of the program altered to take into account the range of radiation exposures that were of interest to NASA?

Dr. **BARR**. To my knowledge, absolutely not.

Mr. **GORE**. So what you are saying is that it was simply piggybacked and that the design of the exposures were made purely with the clinical considerations in mind and it was coincidental that they happened to be within the range that NASA had an interest in?

Dr. **Barr**. Yes.

Mr. **Gore**. All right.

Now, in this same memorandum that I referred to earlier, Dr. Andrews, who is deceased—and I understand that he was quite an individual—all of those who have commented on all sides of this issue, even those who have been critical of this program, speak in respectful tones of Dr. Andrews. I did not have an opportunity to know him, but evidently he made quite an impression on people.

At any rate, he says in this memorandum:

> Other points came up for some mention. One of these was the plan so enthusiastically discussed with me late in November by Evelyn Repplinger to use prisoners in a prison in California for radiation experiments. It seems that there is a Dr. Chen, who has some special relationship to the Governor of California and has a situation where prisoners could be used for all sorts of experiments. The implication was that the radiation experiments could be worked in without publicity as a part of some nutrition studies.
>
> I told Miss Repplinger that I was extremely skeptical about the whole idea, that I felt giving low doses of radiation to normals would not prove anything of value, and that giving large doses would be very doubtful from a medical, legal and ethical standpoint. It seemed difficult to dampen her enthusiasm for this, however. I found in Washington that this project is also known to Vinograd and AEC.

Now, Mr. Stofan, do you know anything about that?

Mr. **Stofan**. I have no knowledge of that program whatsoever. The best recollection we can get from going over all the data is that NASA never participated in any such program.

Mr. **Gore**. Did you have any contracts prior to the 1964 with AEC or other Government agencies?

Mr. **Stofan**. Not to my knowledge.

Mr. **Gore**. No other contracts to determine radiobiological sensitivity?

Mr. **Stofan**. To my knowledge, we didn't. I would have to check the record. I would be willing to do that and go back and ask again.

Mr. **Gore**. I wish you would. If you could supply any such records that you find to the subcommittee, I would appreciate that.

Dr. Barr, are you familiar with this matter?

Dr. **Barr**. No; I am not.

Mr. **Gore**. Well, it is significant for a number of reasons. First of all, because the head of the medical division at Oak Ridge is refusing a suggestion from evidently a NASA employee to irradiate normal human beings and to collect data, and second, because it illuminates partially the relationship between the two agencies, and it would appear, Mr. Stofan, that NASA was actively pushing this idea. You have said already that you don't have knowledge of it, so I don't guess you can respond to this.

[The information follows:]

> A review of the sparsely available records and discussions with individuals indicates that NASA had the following agreements with AEC prior to 1964 to determine radiological sensitivity.
>
> 1. Interagency Agreement No. R77 (10) to support biotechnology and human research required for calculating radiation absorbed dose and roentgens equivalent man dose in human phantoms as a function of radiation energy.
> 2. Interagency Agreement No. R4-1 to conduct biological research with heavy ion beams.
>
> In fiscal year 1964, the following agreements were entered into:
>
> 1. Interagency Agreement No. R104-09 to conduct a retrospective study of radiation effects.
> 2. Interagency Agreement No. R104-04 to conduct human blood irradiation experiments in conjunction with the Gemini missions.

No records have been located of the agreements NASA might have had with other Government agencies to determine radiobiological sensitivity. Due to the timing of the agreements listed (Fiscal Year 1964 and before), no data beyond the agreement number and subject is available in the records currently held.

Mr. WALKER. If I may interrupt. Have we clarified if the employee we are talking about here was a NASA employee? Do we on the subcommittee know that to be a fact? I didn't hear any of the witnesses testify to that. I just want to make certain that if we are targeting NASA or whoever, I think it is important for the record we know who that employee, really works for.

Mr. GORE. It is, and we ought to pin that down for the record. I am attempting to target the truth of this matter, rather than the agency involved. In the memorandum, Miss Repplinger is referred to in the same context with Dr. Billingham, who has been identified as a NASA employee, and it mentions the conversation with Dr. Billingham and Miss Repplinger about NASA's role in this matter.

I think it is a fair inference she is a NASA employee. We will pin that down for the record. I apologize for that hole in the chain of evidence there, but this memorandum surfaced rather late in the subcommittee's inquiry and I have not pinned that down.

Now, Dr. Burr, you refer in your statement on page 2 to multiple objectives of the medical division, one of those being the effort to develop beneficial applications of radiation and radionuclides.

Dr. BURR. I probably need to clarify that. I am talking about the Division of Biology and Medicine's overall multiple, program objectives. Dr. Edington, in his statement, grouped the objectives into two categories: one understanding the effects of radiation, and a second objective that was placed on AEC under the act and that was to develop the beneficial applications of radiation and radionuclides for mankind.

I believe it was in support of that beneficial objective that this program got started, although its initiation preceded my employment with the AEC. The establishment of these hospitals that Dr. Bibb referred to was primarily to utilize radiation and radionuclides for man's benefit in medicine. That is the point I was trying to make.

Mr. GORE. Now, it is fair to say that prior to 1964 there were dual goals at the medical division. One was the treatment of patients and the search for experimental or new cures for the diseases that the patients had, and the second goal was the collection of radiobiological data to determine the parameters of man's radiosensitivity. Dr. Bibb, is that a fair statement?

Dr. BIBB. Yes; I think that is an accurate statement.

Mr. GORE. So there were dual goals before NASA came on the scene?

Dr. BIBB. Absolutely.

Mr. GORE. So after 1964, the secondary goal of data acquisition became more focused, and in addition to the general radiobiological data acquisition, you were also looking for data of a specific kind. Correct?

Dr. BIBB. Mr. Chairman, I think that may be a bit unfair. In my testimony I tried to highlight a significant event that occurred in 1958, which was the accident at the Y12 plant. At that time we found that our knowledge of the biological effects was rather severely limited from the standpoint of being able to measure dose right away. One of the things we began to look for was the biological monitors, that is, were there things you could find in someone's blood that would give you an idea, in an accident, of how much radiation they had been exposed to.

In the Y12 accident, the film badges were unreliable and presented the ORINS group with a terrible challenge in medical management. So from 1958 on, Dr. Andrews, because of the realization that film badge data was so unreliable and since he was turned to in almost every accident, began to look very carefully for any hematologic monitors he could find.

So I would say that data acquisition activity was ordered. I don't want to imply that order didn't occur until the NASA study got started. Beginning in 1958, Dr. Andrews was looking very methodically at hematologic markers that could be used in an accident.

Mr. GORE. I didn't mean to imply that the secondary goal of data acquisition prior to NASA was disorganized.

Dr. BIBB. All right, sir.

Mr. GORE. It had a specific focus because of the Y12 facility accident. It also had the goal of collecting radiobiological data generally, correct?

Dr. BIBB. Yes, sir.

Mr. GORE. Now, a second focus of that data-collection activity was added when NASA entered the picture in 1964, correct?

Dr. BIBB. Second focus, I think, would be a fair characterization.

Mr. GORE. OK.

Now the critical question, again, around which this entire investigation revolves is, were the treatments for the patients altered in order to satisfy or facilitate the acquisition of the data?

Dr. BIBB. Mr. Chairman, I don't believe that to be the case. I have said it many times, and I am pleased to say it under oath. I think Dr. Burr, who was as close to the activity as I was at the time, could respond to that also as a physician.

Dr. BURR. I agree with Dr. Bibb and the statements made earlier. I don't believe that to be the case.

Dr. BIBB. Mr. Chairman, if I could clarify one point.

Mr. GORE. Sure.

Dr. BIBB. One of the problems we were confronted with very early on was the need for reliable human data. We didn't do experiments on people. There had to be a medical purpose, and some benefit for the patient. Our purpose in all those years was to collect data from humans following therapeutic exposures. We worked hard to collect all available data because that was the data we had to use to extrapolate effects. I think it was a well-ordered, well-thought-out program to try to tie animal data to human data.

NASA's requirements were such that additional costs had to be incurred by AEC to meet data needs. And it was those costs that NASA paid for, the additional cost for AEC to collect data beyond that which AEC would have collected or at a rate different than AEC would have collected it.

Mr. GORE. Now, what if you had three possible treatment protocols and one of them would satisfy the data acquisition goal and the other two would not but it was of little difference to the patient as between the three or a judgment call as to whether one was better than the other; would it be all right to choose the one that satisfied the data acquisition goal?

Dr. Bibb. Mr. Chairman, that is the root of the whole ethical question. I think that is a question that a physician would have to answer on a case-by-case basis.

Mr. Gore. Yes. Well, we have some ethicists who are testifying last on the panel, on the witness list. But it is more than just a case-by-case basis, because the design of the entire program is called into question and it has to be addressed in that context. At any rate, my colleague, Mr. Walker, has clarified the record here by finding a specific reference to Miss Repplinger as a NASA employee at the Space Center in Houston.

I would like to yield now to Mr. Walker.

Mr. Walker. Thank you, Mr. Chairman.

Let me clarify something here with everyone just to put the statement from NASA together with what the rest of you said. Is there anyone on the witness panel who would disagree with the NASA statement that NASA did not select any of the patients? Is that something which all of you would agree?

Dr. Bibb. We would agree that they did not select the patients. Was that the question, sir?

Mr. Walker. Yes; it is correct to say that NASA did not select patients.

Dr. Bibb. Yes, sir.

Mr. Walker. Would you also agree that they did not provide input on treatment of patients?

Dr. Bibb. Yes, sir.

Dr. Bur.. Yes.

Mr. Gore. Will my colleague yield on that point?

Mr. Walker. Glad to.

Mr. Gore. We will get into this with the next panel, but the specific course of treatment for each patient was determined by a committee, was it not, Dr. Bibb?

Dr. Bibb. That is my understanding, Mr. Chairman, by the Medical Committee.

Mr. Gore. And one member of the Medical Committee was being paid principally by NASA; is that correct?

Dr. Bibb. Yes, Mr. Chairman, the implication is that he was always there. I think testimony will show that he was very rarely there.

Mr. Gore. He was very rarely there, and I think the evidence supports that, he was there on occasion.

Dr. Bibb. Yes, sir.

Mr. Gore. And was paid by NASA.

Dr. Bibb. Mr. Chairman, in our contract organizations, such as ORAU, their paychecks will all say ORAU. In many cases, the employee really doesn't know what portion of his check comes from what, because the funds are all AEC funds.

I think for clarity it is better if we don't say paid by NASA, because they weren't. They were paid by AEC, who was reimbursed by NASA and the checks said ORAU. I think you would find the employees would say, "My checks are ORAU, that is who paid me."

Mr. **Gore**. That may be the case, but the money came from NASA for that person's salary?

Dr. **Bibb**. Was reimbursed by NASA.

Mr. **Gore**. And earmarked for that person's salary? OK.

Mr. **Walker**. Well, was it really earmarked for that person's salary? I think that is an important point. In other words, I gather from what you are saying that this particular person was an employee of the institution that was operating under a NASA contract, NASA was paying the institution who in turn was paying the employee; is that what you are saying?

Dr. **Bibb**. That is not quite true, Mr. Walker. It was under an AEC contract. All of the work was done under an AEC contract, and only the AEC costs in excess of what we felt AEC should pay for were reimbursed by NASA.

Mr. **Walker**. It is a key point. Who was paying this person's salary that the chairman referred to; was he a NASA employee or was he an employee of the institution?

Dr. **Bibb**. In actuality, the percentage of his salary was such that it would be paid partly by each one. If he were 60 percent NASA one month and 40 percent AEC, it would have been 60-40. But that changed on a month-by-month basis because with our contractors we are paying for a level of effort.

Mr. **Walker**. All I am trying to determine here is if you are talking about who signed the check. Who would he have regarded himself as an employee of? Was he an employee of NASA at any point?

Dr. **Bibb**. ORAU. I guess the question is who could fire him. That would have been ORAU.

Mr. **Walker**. I think that is a key question. Who was his boss and who could fire him?

Dr. **Bibb**. ORAU.

Mr. **Walker**. ORAU.

Let me find out just for a moment here, primarily for my own clarification and clarification of the record, ORAU, are we talking about just one operation here, are we talking just about a hospital at Oak Ridge? What kind of operation is there?

Dr. **Bibb**. Mr. Walker, ORINS, started prior to the AEC, as a matter of fact, to bring about a consortium of some southern universities to make available to the universities the Government facilities which existed in Oak Ridge.

It is today an educational, not-for-profit consortium of some 51 southern colleges and universities. They have been a prime contractor of the Government since AEC was created, primarily in the educational area. The work that ORAU does for AEC, ERDA, now DOE, has primarily been in that area, not in the operating area but in those areas tied more closely to their sponsors. They do far more than operate a hospital, which probably is about 25 percent of the total DOE contract work there.

Mr. **Walker**. Could you give me some idea of some of the best known universities and provide a list of all the universities involved, for the record?

Dr. **Bibb**. I would be glad to do that. On page 4 of my testimony, I gave a list of the university members at the time this hospital was started. I can read those very quickly if you like.

Mr. Walker. I see them. Could you provide a list also for the record of the universities that are presently participating that might go beyond that list?

Dr. Bibb. I would be pleased to, sir.

[The list follows:]

ORAU Member Institutions

University of Alabama
University of Alabama in Birmingham
University of Arkansas
Atlanta University
Auburn University
Baylor University
Catholic University of America
Clemson University
University of Delaware
Duke University
Emory University
Fisk University
University of Florida
Florida State University
University of Georgia
Georgia Institute of Technology
University of Houston
University of Kentucky
Louisiana State University
University of Louisville
University of Maryland
Meharry Medical College
Memphis State University
University of Miami
University of Mississippi
Mississippi State University
University of Missouri
University of New Orleans
University of North Carolina
North Carolina State University
North Texas State University
University of Oklahoma
Oklahoma State University
University of Puerto Rico
Rice University
Southern Illinois University at Carbondale
Southern Methodist University
University of South Carolina
University of Tennessee
Tennessee Technological University
Texas A&M University
University of Texas at Austin
Texas Christian University
Texas Woman's University
Tulane University
Tuskegee Institute
Vanderbilt University
University of Virginia
Virginia Commonwealth University
Virginia Polytechnic Institute and State University
West Virginia University
College of William and Mar

Mr. Walker. Fine. Thank you.

Mr. Stofan, in your testimony, you say flatly in it that NASA was interested only in acquiring data from adult human radiation exposure.

Mr. Stofan. That is correct.

Mr. Walker. Now, that is pretty specific. Would you have objected to data and would you have considered withdrawal of a contract where you were collecting data from an obviously undesired patient? In this particular instance we are talking about a child. That would not fit your criteria at all. Would NASA at that point have considered withdrawing the contract?

Mr. Stofan. I don't know about withdrawing the contract. To the best of our ability to reconstruct the record, NASA was provided data that gave the age of the patient and the rate of the dosage. The best we could find out was that there were no adolescents in the data base that we were given.

Mr. Walker. In other words, you have no record that you ever received any radiation data regarding the Sexton boy?

Mr. Stofan. My understanding is the data was provided, say, age and radiation dose, there were no names provided to NASA of any patients whatsoever. And in the list, the latest list we got we would be able to go through, there were no adolescents in the list.

Mr. Walker. So the only data that you ever received was data that regarded adult subjects, is that your testimony?

Mr. **Stofan**. That is correct; to the best that we can reconstruct the record, that is right.

Mr. **Walker**. And there is no record that NASA received any data relating to pediatric care?

Mr. **Stofan**. There is no record that we have been able to find that relates to that at all.

Mr. **Walker**. Now, if that is the case, the chairman was concerned about records that do not exist at the present time. Is there any chance that records of that type no longer exist and have been destroyed somewhere along the line?

Mr. **Stofan**. I don't know, but I don't think so. Again, when we wanted to get the records to review them, we also went to AEC and they were kind enough to provide them. Their records are better than anyone else's and seem to be fairly complete.

Mr. **Walker**. What you are saying is you have gone back and reviewed the AEC records of what AEC sent to NASA, and in those records there is no indication that AEC ever transmitted any information to you of radiation treatment of children.

Mr. **Stofan**. To the best of my knowledge, that is correct.

Mr. **Walker**. Would such information, had it been transmitted to you, have been of any use to you whatsoever?

Mr. **Stofan**. It would just be speculation on my part; however, I would think not. We were interested in the protection and understanding of what happens with astronauts. So, we would be interested in the data on adult population.

Mr. **Walker**. And data relating to whole body radiation of a child would give you considerably different feedback than whole body radiation of an adult; is that a fair statement? That would be the reason why it would not be of any particular use to you?

Mr. **Stofan**. I would think so. You are in a field where I am not competent to answer the question.

Mr. **Walker**. And for some of you who are familiar with the program: Is that a fair statement? That the kind of information NASA was seeking in terms of whole body radiation was for adult males? And they would get considerably different data if they were given data collected from the whole body radiation of a child?

Dr. **Burr**. Certainly NASA's primary interest was in astronauts, therefore in the age bracket one would expect astronautics to be in.

Dr. Bibb, do you want to comment further?

Dr. **Bibb**. The short answer, sir, is yes.

Mr. **Walker**. In other words, the data they could extrapolate from that would be almost useless to them; is that a correct statement?

Dr. **Bibb**. Yes, sir.

Mr. **Walker**. I have no further questions at this time, Mr. Chairman.

Mr. **Gore**. In other words, the data submitted to NASA pursuant to the contract did not include Dwayne Sexton?

Dr. **Bibb**. That is correct, sir.

Mr. **Gore**. All right. Now, what about this 1974 AEC review, Dr. Bibb?

Dr. **Bibb**. Mr. Chairman, if I could just take a minute to build a little bit of background. As I indicated in my testimony, it was becoming clear to the AEC that the ORINS hospital was becoming very, very expensive to operate. It was small and there was not a large patient base.

By the late 1960's and early 1970's it was no longer unique because the facilities that we had built at ORINS over the years were now duplicated in many other hospitals around the country, particularly major medical centers.

Basically, we were faced with several decisions, one of which was to build a new hospital. That was the driving force behind the so-called 1974 review. The basic charge was to go to Oak Ridge and find out if we should, in fact, build a new facility. The reason for the urgency was that the Oak Ridge hospital of the United Methodist Church was building a new wing and was not going to finish the basement floor.

If the AEC were going to build a new hospital, it had the opportunity to complete that basement floor into an AEC hospital.

The AEC committee found that the existing facilities were not as good as they should have been. I tried to give some history of that in my testimony by pointing out they were still 1943 facilities, AEC-owned and renovated them with AEC funds when those funds were available. The bottom line of the 1974 review was basically that the program in some aspects should continue, the clinical program should not.

Now, there was one main problem, Mr. Chairman: To close an AEC hospital that had been operating as that hospital operated in a town as small as Oak Ridge was not without some trauma. I would have to characterize in some cases the reviewers statements as being overstatements in order to accomplish what we felt should be accomplished, knowing full well that closing down any Government hospital is hard, closing down that hospital was extraordinarily hard. It enjoyed an enormously popular reputation and the people in the community were very fond of it. It was a very traumatic thing to do. I know that first hand so well since that was essentially the first thing I had to do when I moved to the Oak Ridge Operations Office.

Mr. GORE. Without objection, we will put the AEC review data dated May 9, 1974, into the record.

[The AEC review data follows:]

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UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

May 9, 1974

James L. Liverman, Director
Division of Biomedical and
Environmental Research

PROGRAM REVIEW OF THE MEDICAL DIVISION OF OAK RIDGE ASSOCIATED UNIVERSITIES

The following considerations have led to a proposal to change the structure of the program in the Medical Division of ORAU.

1. Oak Ridge does not have an appropriate demographic base with tertiary hospital facilities and a range of active programs in clinical investigation.

   The present clinical facilities of the Medical Division do not meet the standards necessary for accreditation.

   On the basis of program evaluation and institutional environment, it was recommended that clinical investigation should not be continued at ORAU Medical Division.

2. The nuclear medicine program and parts of the clinical oncology program could be incorporated into the East Tennessee Cancer Center at the University Memorial Hospital in Knoxville.

   This would strengthen the development of the Cancer Center and provide the necessary environment for Medical Division programs.

3. The immunology and biochemistry programs of the Division are geographically, operationally and intellectually isolated in the present ORAU structure.

   These programs would be more effective in association with the ORNL Biology Division.

4. The Medical Division of ORAU has been effective in conducting educational programs for physicians in management of radiation accidents and in assessment of radiation damage in man. These programs should be continued and perhaps associated with the capability to develop regional plans for the contingency of industrial exposure and accidental release of radioactivity.

Exploration of the feasibility and implication of these propositions should be started in negotiations with representatives of the concerned institutions. Several issues should be addressed:

1. The cost of providing adequate space and facilities in the Cancer Center in Knoxville.

2. The attitudes of the staff at ORAU and Knoxville concerning the amalgamation.

3. The cost and extent of new facilities in the Oak Ridge Hospital that would serve as demonstration and instructional areas for radiation accident programs.

4. The impact of the proposed changes on other components of the ORAU program.

5. The need to satisfactorily relocate personnel in the ORAU Medical Division.

6. The ability of ORAU to mount a broad program in the sociology, epidemiology and contingency planning related to accidental exposure of human populations to radioactivity.

Charles E. Carter, M.D.
Manager, Biomedical Programs
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Environmental Research

UNITED STATES
ATOMIC ENERGY COMMISSION
WASHINGTON, D.C. 20545

April 16, 1974

ORAU REVIEW

For several years there has been growing concern over institutional and programmatic problems of the Medical Division of ORAU. The discussion of these problems which follows is based upon the comments of reviewers who visited the laboratory on March 4, 5 and 6, 1974.

A. The Institutional Setting

1. The clinical facilities are substandard with respect to licensing and accreditation guidelines and replacement is sought by ORAU through new construction in a wing of the Oak Ridge Hospital.

2. The Medical Division conducts an investigative program in an area of relatively low population, in the absence of a tertiary hospital program adequate for the provision of specialized patient populations and services, and essentially isolated from the critical climate of academic clinical investigation.

3. The laboratories in the main building vary from adequate to marginal and are housed in a structure originally designed for other purposes and a short life time. The marmoset building contains good, permanent laboratories and the biochemistry building is considered to be sound and provides good laboratory facilities. The separation of these facilities makes effective interaction of professional personnel and the synergistic development of programs virtually impossible.

4. The animal facilities are separated in several buildings and except for the marmoset building all are considered to be strikingly inadequate with respect to construction, provision of animal care, quality control, separation of species, and sanitation. The animal care programs suffer from lack of professional supervision.

B. Programs

The several programs in the Medical Division vary widely in quality.

1. Clinical Hematology. The reviewers gave this program an unfavorable rating.

   a. The METBI and LETBI programs were viewed as evolving without adequate planning, criticism or objectives, and have achieved less in substantial productivity than merits continued support.

   b. The marrow transplantation program came under severe criticism. In view of accepted therapeutic modalities, ethical questions were raised with respect to the protocols employed in these studies. The leadership of this program is not defined; the coordination with immunology is ineffective. The number of patients accessible to the study is small and argues against the continuation of transplant clinical investigation at ORAU.

2. Nuclear Medicine

   a. Radiopharmaceutical program. It was recognized that Dr. Hayes had demonstrated a high degree of capability and achievement. Questions were raised about the scope and directions of the ^{11}C project, the absence of physical chemical data on Gallium complexes, and a discernible tendency for the program to drift without defined goals. The isotope production facility at ORNL is an asset to the program, but in order to be effective, a significant nuclear medicine clinical facility at a large teaching and research hospital is necessary. The program suffers by its present isolation.

   b. Clinical program. The number of nuclear medicine procedures performed is small and the interaction with Oak Ridge Hospital is minimal. The reviewers recognized Dr. Edwards' clinical competence and the dedication which he has brought to the program. There were questions about the design and evaluation of the Gallium cooperative study which limit the value of the collected data. The bone-scan investigation of Dr. Goswitz received unfavorable review comments.

3. Immunology. The reviewers gave this program top rating. Dr. Gengozian was recognized as a productive, innovative worker with well-defined research goals. It was recommended that increased support should be directed to this group.

4. Biochemistry. The projects under Dr. Snyder's direction were considered to be of high priority and productive of significant achievement. It was felt that he was intellectually, as well as geographically, isolated from the Medical Division. The reviewers raised the question of whether Dr. Snyder might not have more productive interactions in another laboratory setting.

5. Computer Services. This program is under the administrative control of Mr. Harmon, Dr. Andrews' administrative assistant, an arrangement which reviewers considered to be inappropriate for effective development of these facilities. In 1968 an IBM-1800 with peripherals was purchased. In 1972 a PDP-11/20 was brought in, and since then there have been efforts to interface the computers. This system is not good computer science. An effort to use virtual memory concepts with the disc through the IBM-1800 and the change of the system from time sharing to multi-programming are laudable efforts, but not essential to any scientific program at ORAU. Interface attempts to the Ohio Nuclear Scanner and the gamma camera were questioned because the investigators lack sound notions as to what is to be done with the encoded data. Ideas of image enhancement and quantitation were not well thought through. Other critical comments of the reviewers related to the inappropriateness of a patient information data system for a small clinical service of eight patients per day, and to the random and unproductive interaction of the staff of the computer center with other investigators. It was observed that the use of computer service for the biostatistics associated with the Gallium study and other data analysis programs is appropriate, but could be implemented with or without the present computer hardware.

6. Experimental Pathology. Dr. Swartzendruber, an electron microscopist with considerable experience and achievement, received strong support from reviewers for his work on the biophysics and ultrastructural aspects of Gallium localization in tumors. There was less enthusiasm about his pursuing x-ray spectroscopy and transmission electron microscopy in anything other than collaborative efforts with available instruments at ORNL.

   Dr. Nelson, a pathologist who does the routine work of the center, has recently received training in Germany. The reviewers were cautious in viewing his entry into a demanding and competitive program concerning the distribution and kinetics of labeled circulating stem cells. Although an enthusiastic and careful worker, it was felt that his lack of research experience, training, and scientific achievement might advise a collaborative effort or some opportunity for supervision.

7. Radiation Accidents; Human Radiation Exposure. The broad experience of Dr. Lushbaugh and his achievement in published assessment of human radiation exposure were considered by reviewers to have great value. Although a large part of his research effort is funded by NASA, it was considered to be effectively supportive of AEC missions and well done. It was reported by reviewers that the computer services have not provided adequate consultative treatment on statistical problems. Dr. Lushbaugh's new findings on colonic cancer in one strain of the marmoset were considered by reviewers to be a significant discovery worthy of substantial support.

   Drs. Andrews and Lushbaugh have been an effective team in dealing with problems of radiation accidents.

8. Microbiology. The comments of reviewers were generally unfavorable with respect to this program. The routine microbiology of the clinical services is handled by competent technicians and appeared to be of high quality. Dr. Tyndall was reported by reviewers to have little interest or background in clinical microbiology; as a result, some of the crucial studies of patients with total body irradiation have neither been followed up nor initiated. Dr. Tyndall's studies of Gallium were evaluated as being inadequately planned, isolated from consultation with immunologists and molecular biologists, and not coordinated with the principal responsibilities of the microbiology program.

9. Cytogenetics. Dr. Littlefield was appointed to work with Dr. Goh on a project supported by NIH dealing with cytogenetic effects of oral contraceptives in women. When Dr. Goh left ORAU, Dr. Littlefield became principal investigator and succeeded to responsibility in a study with many methodological problems. Dr. Littlefield was considered by the reviewers to be a technically competent cytogeneticist who had performed creditably, but who had not yet matured scientifically as an independent investigator. It was felt that the Medical Division had not developed a cytogenetics research program, and that much of Dr. Littlefield's effort was spent in unplanned and unused clinical supporting services. Dr. Littlefield has the potential to become a competent independent scientist.

10. Physics and Instrumentation. The work of Roger Cloutier and Evelyn Watson on problems of dosimetry was recognized as having outstanding merit. The cooperative work with Walter Snyder of ORNL suggested that a more suitable association for work on dosimetry might be at ORNL. The work by Gibbs on the whole-body counter is almost entirely in support of dosimetry studies.

    The work of Morris was viewed as instrumentation development proceeding independently of carefully assessed needs for problem solving. The projects were considered to be of low priority.

C. Administration of the Medical Division

In general, the reviewers were unanimous in their judgment that ORAU Medical Division was an institution with a creditable history, but one that is now faced with serious problems. While respectful of the administrative leadership of the division, it was recognized that the institution lacked the cohesion and scientific leadership to overcome the fragmentation of programs, variable scientific quality and inadequacy of clinical setting. These judgments, though strong in advocacy of change, were not made without recognition of the dedication and achievement of Dr. Andrews in a formidably difficult situation.

Recommendations

A. Clinical Research Programs

The proposed construction of facilities in the Oak Ridge Hospital will not provide the clinical setting necessary for the development and sustenance of a clinical research program in nuclear medicine, radiotherapy and clinical oncology. There are several options to be considered.

1. Phase out programs in clinical research.
2. Disperse those clinical programs with good competitive standing to regional University Medical Centers for independent funding.
3. Transfer programs in nuclear medicine and oncology to the East Tennessee Cancer Center at the University of Tennessee Memorial Hospital in Knoxville.
4. Concentrate on a nuclear medicine program at Oak Ridge which places little emphasis on clinical research and heavy emphasis on basic mechanisms, isotope production and instrumentation development in association with Oak Ridge National Laboratory.

These options were proposed and discussed in some detail by our reviewers. The concensus supported the consolidation of clinical research and supporting programs, such as experimental pathology, with the University Hospital and Cancer Center in Knoxville. Such a development would considerably strengthen both institutions.

At this time, all of the factors which will influence decisions in the several institutions involved are not known; and we view this recommendation as an opening move in a series of negotiations, many of which depend on the status of the Cancer Center program at Knoxville.

B. Radiation Accidents and the Social Strategy for Dealing with Human Exposure to Environmental Radiation

1. The extensive experience of Drs. Lushbaugh and Andrews in problems of radiation accidents argues for supporting a facility in Oak Ridge which would consist of a demonstration unit in the Oak Ridge Hospital with laminar flow rooms and a decontamination area suitable for treatment of accident subjects. This facility would serve as a focus for a teaching program addressed toward physicians and public health officials who are charged with responsibility in environmental health planning.

2. The above program should be coordinated with a sociological research and assessment program at the ORAU campus which would address problems of preventive and response planning for environmental contamination resulting from accidents and nuclear fuel release. This program might develop with well-defined relationships to the "think tank" for energy options which ORAU has initiated.

3. It might also be appropriate at this time to think about centralizing the information processing and some components of the human epidemiology programs relating to occupational exposure and health assessment of workers at a facility such as that proposed for ORAU. The computer center now serving the Medical Division might then be transferred and restructured to serve this function.

C. The Immunology Program and the Biochemistry Program should be brought into administrative association with ORNL and as soon as feasible into that laboratory. The strength of these programs and the adequacy of present facilities is recognized, and alternative options might be considered.

D. The Medical Physics and Instrumentation Program would be more appropriately developed in ORNL. The recognized merit of Dr. Cloutier's work in dosimetry would undoubtedly lead to the possibility of incorporating his program into a combined effort at the Cancer Center, University of Tennessee Hospital in Knoxville, should this proposition be developed.

E. In recognizing the potential of Dr. Littlefield to develop as an independent investigator in cytogenetics, a transfer of her program to the cytogenetics group at ORNL is recommended.

F. The Microbiology Program might be identified with several institutions; at this time no recommendation is made.

In making these recommendations, there is recognition of the dislocation and discomfort they entail. There is a determination, however, to deal sensitively and considerately with the people involved. At the outset it should be realized that we are embarking on a series of meetings with several concerned parties; we propose several recommendations to orient the discussions. With considerable firmness we respond to the recommendation of our reviewers and our staff that the present configuration of the Medical Division of ORAU must change.

As a consequence of these recommendations, certain actions with respect to construction of facilities are entailed.

1. ORAU and AEC should not enter into an agreement with Oak Ridge Hospital for the construction of a 26-30 bed clinical facility.
2. The possibility of a demonstration accident treatment facility with an attached decontamination unit as part of the new construction being planned at Oak Ridge Hospital should be explored. This facility might contain two laminar flow rooms, offices and a conference area.
3. There should be no new construction of animal facilities.

The changes resulting from these recommendations should take place over a period of two to three years.

Mr. GORE. As has been noted previously, it does contain some harsh conclusions.

Dr. BIBB. I am prepared to respond to those, Mr. Chairman.

Mr. GORE. I understand. It is dated, actually, April 16, 1974, the cover letter is May 9, 1974. What you are saying is that for a variety of reasons it was time to fish or cut bait on continued funding and upgrading of this facility. You had to make a decision and you justified the decision with this review, and for that reason the statements, according to your testimony, were harsh, partly for that reason. You are not saying that the report is inaccurate, are you?

Dr. BIBB. No, sir.

Mr. GORE. OK.

Dr. BIBB. I might add that most of the recommendations in that report, Mr. Chairman, have been implemented today. The ORAU program as it exists today is in direct response to that report.

Mr. GORE. When it says that the facilities were substandard with respect to licensing and accreditation guidelines, in what way were they substandard?

Dr. BIBB. Primarily they didn't meet the standards which were required for a modern hospital. The patients were on the third floor of a building built in 1943. The facility did not have to meet the State of Tennessee codes, being a Federal facility. However, in order to become an AHA accredited facility which would be able to accept third party payments to help cut costs, it would have required major renovations. It was not unsafe by Government safety standards, but it didn't meet the new hospital standards.

Mr. GORE. The subject of isolation is discussed. Wasn't this a longstanding concern?

Dr. BIBB. Mr. Chairman, that has been a concern since the facilities were first located in Oak Ridge. It was a concern at all early AEC facilities including Los Alamos. I think there are two kinds of isolation—intellectual isolation and physical isolation. I would submit that the scientists in Oak Ridge, whether at the National Laboratory or ORAU, were not intellectually isolated. I would agree that they were isolated from large major medical centers. This presented us with a problem we had to deal with in the later years of the hospital's operation.

Mr. GORE. But the report said it was isolated from the critical climate of academic clinical investigation, unquote. Now, the animal facilities were considered "inadequate with respect to construction, separation of species and sanitation." Was AEC headquarters aware of those conditions prior to 1974?

Dr. BIBB. I am certain we were, Mr. Chairman, but that is fairly judgmental. We have an awful lot of animal facilities in Oak Ridge, and I suppose at any one time one could argue some of our facilities were inadequate. In response to that, we have made major changes in the animal facilities at ORAU. As a matter of fact, the entire third floor has been renovated into a modern animal care facility.

Mr. GORE. Yes. And I have seen that. What about the practice of keeping the mice cages suspended on plastic cords in the open space behind the LETBI patient care room; did that cause you concern?

Dr. BIBB. Mr. Chairman, I think every precaution that could be taken, and probably more precautions than were taken in other places, were taken there. As you know, the area was closed in with plastic, wooden frames with plastic around them. It had its own separate ventilation system, outside of the LETBI room. They were separated from the patients I don't think it was an uncommon or an unsafe practice in any sense.

Mr. GORE. What about the transporting of the animal cages, and animal wastes in plastic bags through the area where patients traveled?

Dr. BIBB. Mr. Chairman, that sounds more graphic in writing than it was in reality. As you know, the space we are talking about could be 6 feet, 8 feet, possibly, as you come up from below LETBI into a short corridor, across the corridor and out a door to the outside. The patient area at that time was down the corridor the other way some 15 to 20 feet, minimum. The wastes were sealed in plastic bags before any material was brought out of there. I don't believe there were any unsafe or hazardous conditions as far as the patients were concerned.

Mr. GORE. OK. We will ask the next panel about this also.

Now, the actual radiation facilities, METBI and the LETBI, were viewed in 1974 AEC report as "evolving without adequate planning, criticism, or objective and achieves less than substantial productivity than merits continued support." Do you believe that accurate or is that one of the statements that you believe was overstated because of the circumstances?

Dr. BIBB. I would have to agree that it may be a bit of an overstatement: "* * * achieves less than substantial productivity than merits continued support" is an extraordinary phrase to really have to explain. I think the meaning is that or ORAU should have put out more papers for the dollars they got. I suppose one could argue that about any research project. I think we all feel they should have published more.

Mr. GORE. What clinically useful data other than blood counts have been derived from the METBI and LETBI programs? Do any of our panelists——

Dr. BIBB. Dr. Burr, I think.

Mr. GORE. Dr. Burr.

Dr. BURR. Would you restate that?

Mr. GORE. What clinically useful data other than blood counts have been derived from the LETBI and METBI program?

Dr. BURR. I think it became clear in comparing the LETBI and the METBI that going to the low dose rate—though it looked like on biological grounds that this might be a good way to go—really didn't significantly improve the situation and it had some drawbacks of its own, particularly the time necessary for radiation. I think perhaps the physicians from Oak Ridge should address this as to what they feel were the major advantages.

Mr. GORE. We will ask them that. I think it should be noted for the record that this same report gave the immunology program a top rating and found that Dr. Andrews and Dr. Lushbaugh had been an effective team in dealing with radiation accidents.

Now, the review also severely criticized the bone marrow transplantation program and said, "In view of accepted therapeutic modalities, ethical questions were raised with respect to the protocol employed in these studies."

Dr. **Bibb.** Mr. Chairman, that is a very tough technical area, and I am aware of the basis for that comment of one reviewer. If Dr. Hubner and Dr. Vodopick could respond to that, it would probably mean more to the record and to the committee.

Mr. **Gore.** All right, we will ask the clinicians that question.

Mr. Stofan, how often did NASA receive briefings from the Oak Ridge Medical Division?

Mr. **Stofan.** In looking through the record, they were unable to establish how often, but I assume it would be frequently. That data wasn't available.

Mr. **Gore.** Was it generally in person, orally, or in writing?

Mr. **Stofan.** I don't have the knowledge of how it was done, but I think one could assume it would most likely be in both ways. That is standard practice.

Mr. **Gore.** Can some of our other witnesses tell us the answer to that?

Dr. **Barr.** I cannot.

Mr. **Edington.** I cannot.

Mr. **Gore.** There were quarterly progress reports written by AEC and provided to NASA. In addition, there were oral briefings; is that correct, Dr. Bibb?

Dr. **Bibb.** Yes, sir. There were joint meetings, at least there were some joint meetings, because we have records of those.

Mr. **Gore.** Now, NASA provided how much money totally to the Oak Ridge Medical Division, Mr. Stofan?

Mr. **Stofan.** NASA did not provide money to the Oak Ridge Medical Division. NASA provided, I think I stated, $2.2 million to AEC.

Mr. **Gore.** $2.2 million to AEC for the Oak Ridge Medical Division; correct?

Mr. **Stofan.** Yes, that is where the study was conducted.

Mr. **Gore.** Now, that money was used in part for the bioinstrumentation for monitoring patients in the LETBI facility, among other things; correct?

Mr. **Stofan.** That is correct.

Mr. **Gore.** That consisted of the belt that was placed on patients; correct?

Mr. **Stofan.** Yes. I am not particularly familiar with the belt, but it was the biomedical instrumentation and I would assume that was in the form of a belt.

Mr. **Gore.** OK.

Now, the person who monitored the belt was paid 100 percent by NASA; is that correct?

Mr. **Stofan.** I have no knowledge of that whatsoever.

Mr. **Gore.** Well, I don't think it is an unfair question.

Mr. **Stofan.** My best understanding is that the money was—maybe we are getting into semantics—transferred from NASA to the AEC. The AEC then paid the people at ORINS. My understanding is that, indeed, some of the doctors involved and some of the technicians' salaries were paid as a result of transfer of funds from NASA to the AEC, but none of these people was on the NASA payroll.

Mr. **Gore**. Dr. Bibb, can you help us with this?

Dr. **Bibb**. Yes, sir; that is correct. The technician's salary was reimbursed 100 percent from NASA. But I might add further that any proposal to NASA usually would indicate certain types of people and certain types of percentages, but the ultimate decision on how the percentages would be spread would have been a decision of the contractor. Remember, these are management-type contracts. We do not try and tell the contractor how to use the people under the contract.

Mr. **Gore**. Now, Anne Sipe was the technician——

Dr. **Bibb**. Yes, sir.

Mr. **Gore** [continuing]. Who monitored the readouts from the belt, was paid 100 percent from the NASA funds?

Dr. **Bibb**. That is my understanding.

Mr. **Gore**. That is correct?

Dr. **Bibb**. Yes.

Mr. **Gore**. Now, Dr. Lushbaugh was paid partly with NASA funds and partly with AEC funds?

Dr. **Bibb**. Yes, sir.

Mr. **Gore**. In the early years, beginning in 1964, about 15 to 20 percent of his salary came from NASA, but that percentage increased until a couple of years later it was close to 90, 95 percent, 100 percent?

Dr. **Bibb**. Mr. Chairman, I will have to accept that because I really don't know.

Mr. **Gore**. Well, OK. I ask you and I will ask Dr. Lushbaugh on the next panel. But I know he has said that he and others looked upon themselves just as part of the same team and he may not be familiar with the exact evolution of that percentage. But I believe the record will show that it began at 15 percent and then steadily rose to close to 100 percent.

Now, at one point AEC reports to NASA that it is going to take active measures to try to increase the utilization of the radiation facilities. Dr. Burr, was the number of patients run through the radiation facilities, affected by the desire to fulfill the NASA contract?

Dr. **Burr**. The use of radiation therapy, to the best of my knowledge, and how it would be used for an individual patient, was in the hands of the medical staff, as to what they thought would be the best.

Mr. **Gore**. OK, that again will be——

Dr. **Burr**. So I don't think I can really comment.

Mr. **Gore**. That, again, will have to be addressed by the next panel.

Dr. **Bibb**. That depended on several things. No. 1, it depended on funds provided by AEC for the clinical program, and No. 2, it depended upon the types of illnesses that were referred to ORAU by the referring physicians. So these remarks, Mr. Chairman, are coming from proposals, where the contractor is saying if AEC gives us the money we requested for our clinical program, we will have more patient data that we will be able to analyze for the NASA program." It is not saying, "NASA, if you pay more you will get more data."

Mr. **Gore**. No; I didn't mean to imply that. It is a critical difference and I appreciate the clarification.

Dr. Burr and Dr. Bibb, did the two of you notice any trends over the period of years involved? Did you specifically notice the trend which was referred to by Dr. Heyssel?

Dr. **Burr**. Can you be a bit more specific?

Mr. **Gore**. Mr. Heyssel told us that in his judgment, in the early years this facility was way ahead of other facilities but that because of the development of research capability in the rest of the country that changed and it fell behind in the later years.

Dr. **Burr**. I think you have to say, Mr. Chairman, that initially there were very few centers that could provide this kind of training for physicians and for scientists. And as I pointed out in my testimony, this was certainly one of the major accomplishments of this group: The capability of training new people in this area.

And as the information was disseminated through training certainly at medical centers—these individuals who went back trained others and the whole knowledge of the field was further disseminated and, at least in this capacity, their role tended to be somewhat reduced. In the area of research the medical centers began to pick up these tools and to move ahead too. I think that is also true. That doesn't mean that the work that continued wasn't of equal importance. It means there were more centers capable of conducting work in these areas.

Mr. **Gore**. OK. Mr. Walker.

Mr. **Walker**. Just briefly to sum it up, in my own mind anyhow, as I understand it, in terms of NASA's involvement here from your testimony, Mr. Stofan, I gather that the total program amounted to about $26 million, and of that $26 million NASA provided approximately 10 percent of the money, or $2.2 million?

Mr. **Stofan**. That is correct.

Mr. **Walker**. And included in that total would be the fact that you provided some of the equipment that was used. You helped reimburce the pay certain personnel within the center through the contract that you had with AEC, and I assume that some things like heat, light, and all of that sort of thing were paid for with your portion of the contract too, that that's what it is all about?

Mr. **Stofan**. That is correct.

Mr. **Walker**. So, in terms of the experimentation that went on, you were only a data receiver based upon money that you put in, but I gather that you did not initiate patient treatment, you did not select patients and so on. Is that a fair summation?

Mr. **Stofan**. That is a very fair summation.

Mr. **Walker**. Thank you.

Mr. **Gore**. All right.

I would like to thank all of you for appearing here today. Thank you very much. Any of you have anything to add?

[No response.]

Mr. **Gore**. Before our next panel, since we have only one court reporter with us here today, I would like to take a 5-minute break for his benefit and for the benefit of others.

[Recess.]

Mr. **Gore**. The subcommittee will come back to order.

Our witnesses are Dr. C. C. Lushbaugh, chairman, Oak Ridge Associated Universities, Medical Division, Dr. Frank V. Comas, chief, Department of Radiation Oncology, University of Tennessee Memorial Hospital, Dr. Helen Vodopick, Oak Ridge Medical Clinic, Dr. Karl Hubner, chief, outpatient nuclear medicine, and Ann Sipe, LPN, former lab technician.

Ladies and gentlemen, if you will stand and raise your right hand.

[Witnesses sworn.]

We would like to begin with you, Dr. Lushbaugh.

TESTIMONY OF DR. C. C. LUSHBAUGH, CHAIRMAN, ORAU MEDICAL DIVISION; DR. FRANK V. COMAS, CHIEF, DEPARTMENT OF RADIATION ONCOLOGY, UNIVERSITY OF TENNESSEE MEMORIAL HOSPITAL; DR. HELEN VODOPICK, OAK RIDGE MEDICAL CLINIC; ANN SIPE, LPN, FORMER LAB TECHNICIAN; AND DR. KARL HUBNER, CHIEF, OUTPATIENT NUCLEAR MEDICINE

Dr. LUSHBAUGH. Mr. Chairman, I appreciate the opportunity the committee has provided me to present factual information concerning analytical studies carried out under my and Dr. Gould Andrews' direction for the Atomic Energy Commission [AEC] with the support of the National Aeronautics and Space Administration under an interagency agreement in force from 1964 through 1974.

Dr. Andrews, now deceased, was chairman of the Medical Division, ORINS, and I was a member of his staff, heading a research group in applied radiobiology, studying the effects of total body radiation exposure on man. I also directed AEC-funded research projects on whole-body counting and red cell sizing among others.

You have heard from previous testimony how the NASA/AEC interagency agreement came to be, its purpose and objectives. Because of my research background and nonclinical interest in assessing the relative radio-sensitivity of animals, including humans, Dr. Andrews assigned me the task of measuring as precisely as possible human radiation dose-response relationships using data obtained from clinical experience with radiation accident victims and patients who had received total body irradiation [BI] therapy in the course of their natural diseases.

This subsequently came to be known as the NASA study. Previous testimony has described for you how these analytical studies were carried out using hospital charts, the results of the analyses and their inclusion in the National Academy of Science book, published in 1967; which still is used worldwide as a reference text whenever questions of human radiation tolerance arise.

I want to emphasize that clinical data on children under 12 were not considered for analysis since the medication given before total body irradiation would have biased any conclusions regarding nausea.

You have also heard the history of the development of the low-dose-rate radiation exposure facility which was designed to extend the clinical use of TBI and hopefully to improve its therapeutic usefulness while decreasing the toxicity common to rapidly delivered radiation exposures.

The use of this facility by the clinical staff in the treatment of their patients afforded the NASA study group the opportunity to observe in real time the signs and symptoms of radiation exposure that we had previously had to study in retrospect from medical histories and charts.

The use of remote surveillance equipment developed by NASA for monitoring astronaut performance afforded the ORINS clinical staff a means of constantly keeping a check on the well-being of the patient being irradiated 20 hours a day in LETBI. It should be noted that patients in LETBI were watched by closed-circuit television and the monitoring was critical when the patient was asleep. This also afforded my staff and me the opportunity to study tapes of these signals [EKG, heart rate, and respiratory movements] to better understand the pathophysiology of the patient.

As you are no doubt aware, 10 years later such equipment became commonplace in the best intensive care units and allowed one nurse to monitor constantly the status of a ward full of seriously ill persons.

It might be expected that the newer LETBI facility would cause the clinicians to shift their therapy plans to its use over that of the older METBI facility where the dose rate was 60 times as rapid.

During the first 2 years of its operation, the clinicians did use the LETBI facility much more often than the METBI. However, after a relatively short while the clinicians went back to using the METBI facility to deliver the so-called LETBI dose of 30 R in 20 minutes instead of the 20 hours required in LETBI.

They found that with the METBI facility, the 30 roentgen/day radiation treatments could be given on an outpatient basis. As a result, in 1973, the METBI treatments numbered 168, whereas in the LETBI unit, the number was only 15.

I have shown these in figures 1 and 2 which I would like to explain at the end of my statement.

Mr. **Gore**. We do have copies of the material you are referring to in your statement.

Dr. **Lushbaugh**. Since the therapeutic effects were the same, and since the METBI fractionated therapy also avoided radiation sickness, the METBI facility proved to be more efficient and more acceptable to the patients. The clinical use of the LETBI facility declined progressively in the last 5 years of its operation and at the time of the closure of the ORAU hospital unit, the LETBI facility was in a standby status.

In light of concerns which have been expressed, I would like to clear up two points.

First, neither NASA, nor AEC people from headquarters who we call program monitors—to my knowledge, ever attempted to become involved directly or indirectly with the treatment of patients at ORINS/ORAU Medical Division.

Second, the ORINS/ORAU NASA study group never influenced the clinicians in their selection of patients or the prescriptions of the exposure dose and dose rates. In fact, I studiously avoided making any such recommendations and Dr. Andrews and his clinical staff never requested such recommendations.

Mr. Chairman, that concludes my testimony. But I would like to explain these two charts which are appended to your handout.

The first one shows the number of treatments per year in the two facilities, the upper one being LETBI, the lower the METBI facility. It shows a time scale going from the year 1958 through 1975. It shows on the Y axis the number of treatments per year in each facility.

As you can see, the LETBI facility starts up in 1967. Previous to that, from about 1960 through 1966 you can see that there were up to 20 to 24 patients in 1 year in the METBI facility. This usage was rather level across time.

In 1967 when treatment in LETBI facility starts—the number of persons treated in the METBI facility decreased to 3, where in the LETBI facility this number went up to about 10. The highest utilization in the LETBI facility reported as number of patients in 1 year occurred in the year 1970 when 15 persons were treated.

You can see starting at about 1970 there was a change apparently in the clinical attitude and the use of the METBI facility began to increase because the clinicians decided that the 30-roentgen-per-day dose could be given in 20 minutes in the METBI facility. It did not require the 20 hours in the LETBI facility which a lot of the patients objected to because it took too much of their time and they found with the METBI the patient could come into the outpatient clinic, see their doctor; the doctor would do his physical exam and blood count and then decide whether or not he needed to have another radition treatment.

If he needed it, he got it with no difficulty and he was able to go home.

If you take a look at the actual number of patients that were treated in the two facilities you can see the number of patients in LETBI declined and never quite get to be as high even in the situtation where we have 168 treatments on the first chart in 1973.

During that time there were approximately seven or eight patients that were being treated in that way. This answers for you I believe some of the questions that you asked previously, and shows that this was the period of progressive decline in the number of patients who were actually entering the Medical Division for this kind of study at this time.

But you can see by number of patients it was an even split between the METBI and LETBI facility after 1972, but whereas the number of treatments that were given was much, much greater in METBI—168 versus 10 in the LETBI facility in 1973.

I believe that illustrates some of the points that you have raised in your previous questions.

[The prepared statement of Dr. Lushbaugh follows:]

STATEMENT BY CLARENCE C. LUSHBAUGH, PH. D., M.D., MEDICAL AND HEALTH SCIENCES DIVISION, OAK RIDGE ASSOCIATED UNIVERSITIES

Mr. Chairman and members of the Committee, my name is Clarence Lushbaugh. I am the Chairman of the Medical and Health Sciences Division of Oak Ridge Associated Universities, formerly known as the Oak Ridge Institute of Nuclear Studies. Before I begin, I would like to introduce my colleagues who are with me today. They are: Dr. Helen Vodopick of the Oak Ridge Medical Clinic, Dr. Frank Comas, Chief, Department of Radiation Oncology, University of Tennessee Memorial Hospital, Dr. Karl Hübner, Chief Clinician and Director of REAC/TS, and Mrs. Ann Sipe, LPN, Radiation Emergency Assistance Center/Training Site.

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Mr. Chairman, that concludes my testimony. I will be pleased to answer questions.

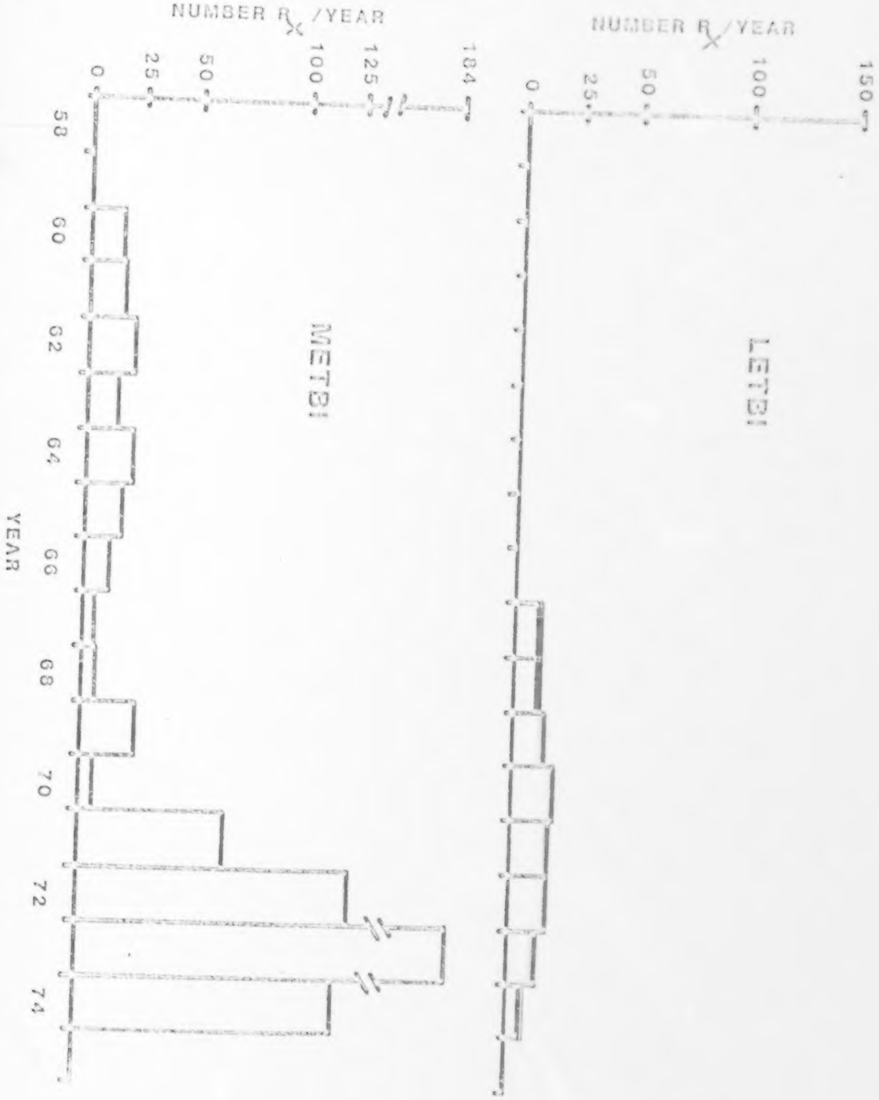
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Figure 1

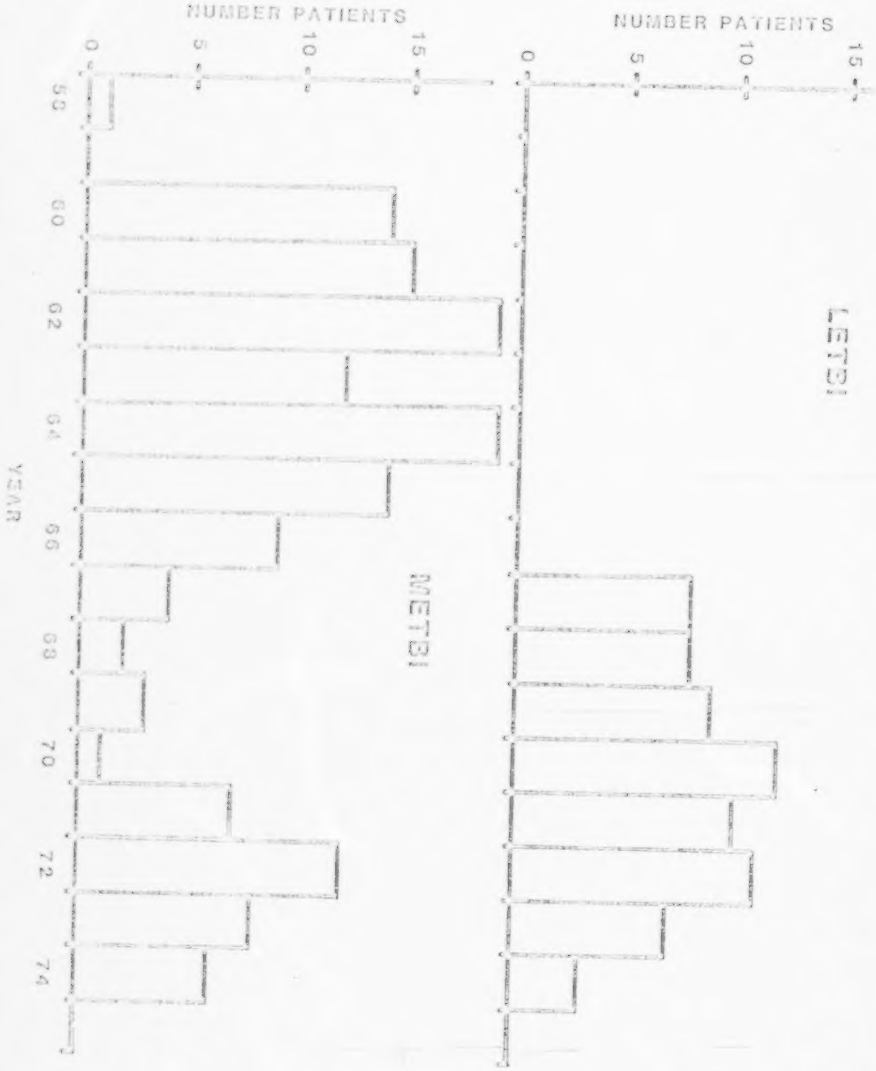
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Figure 2

Mr. GORE. Thank you very much.

We will hold questions until the other members of the panel have completed their statements.

Dr. Vodopick, we will go to your statement now.

Dr. VODOPICK. Mr. Chairman, members of the committee, I am Helen Vodopick, a specialist in hematology and medical oncology in Oak Ridge, Tenn.

From July 1965 to January 1975, I was a member of the clinical staff at the ORINS/ORAU Medical and Health Sciences Division.

In order to evaluate the type of treatment given to patients at Oak Ridge Associated Universities (ORAU) we must turn back the calendar to the late 1950's and early 1960's. At that point in time, the main modalities of treatment of cancer were surgery, irradiation, and very few chemitherapeutic agents. Surgery played the greatest role in the treatment of solid tumors where bulk disease could be removed en masse.

However, such an approach most often failed because the tumor had spread beyond the confines of the surgical field. At times radiation was used as a supplement to eradicate residual disease. Unfortunately, there were also malignant diseases not amenable to surgery. These diseases were either too widespread in the case of lymphomas—tumor of the lymph glands—and inaccessible to surgery in the case of leukemia. Therefore, it seemed logical to control these latter malignancies with irradiation. A new method was devised to administer this irradiation called total-body irradiation [TBI] whereby the widespread disease would be uniformly treated. The investigation of this treatment method became one of the primary goals of the ORAU Medical Division.

The overall radiation program at ORAU was best described by Dr. Gould Andrews, then Medical Division Chairman, in a preface of the 1966 year report of the ORAU Medical Division.

He said:

> This is a long range continuing program which has as its objective the improved treatment of disease by means of radiation, both internal and external. Main areas of effort are, (1) the best use of total-body irradiation in the treatment of lymphoma, leukemia and polycythemia; (2) local external irradiation therapy for certain types of cancer, including application of experimental methods based on animal studies . . .

Since this was a new method of treatment, experimental protocols were developed to evaluate the effectiveness and potential toxicity of this type of irradiation much like protocols now used to assess new drugs in people. Such protocols were reviewed by a human use committee.

Lymphomas and chronic leukemias were already known to be sensitive to radiation given in large doses to localized areas. It was still to be determined what the least dose of total-body irradiation administered at various intervals could be used to control these diseases.

According to protocol, treatment was titrated to the patient's response. The aim and prime intent of this therapy was to control the lymphoma, leukemia or myeloproliferative disorder.

With this intent, only patients with these diseases were accepted to the Medical Division of ORAU for treatment with TBI. These patients were informed of this experimental approach on their initial admission and were required to sign an admission form attesting to this fact.

Submitted with the testimony is a copy of the admission agreement.

In addition, the chief of the medical service would again explain the procedure before its actual implementation. Therefore, the patients were fully informed of the type of therapy and the investigational nature of it.

Children with acute leukemia and lymphoma, 19 and 1 cases respectively, were also accepted for TBI treatment. These 20 children treated between 1957 and 1968 were irradiated in the medium exposure TBI unit. The majority of these children had been treated with drugs which failed to arrest their disease.

It must be remembered that between 1965 and 1969 according to American Cancer Society statistics, the 1-year survival rate for children with acute leukemia under 15 years of age was 40 percent and 5-year survival rate was 3 percent.

Out of context, I don't know where Mrs. Sexton got the 17 percent living at that time. As to this 3-percent survival rate I am not sure either. The statistics prior to that time were even more dismal. Therefore, it was hoped that by irradiating the whole bone marrow with a high total dose the leukemic cells could be eradicated.

Twelve such children were treated in the METBI facility between 1961 and 1968. These children were also treated with chemotherapy. The leukemia was brought under partial control in some cases but reoccurred in all instances. Achieving a remission was possible but maintaining it was not.

Since neither drug therapy nor irradiation had succeeded in curing leukemia in a significant number of children, a new completely different approach was tried. Immunotherapy had worked in animals as proven by Delorme and Alexander. This therapy was based on using a donor's normal sensitized lymphocytes, referred to as killer cells, to attack and kill leukemic cells in a recipient.

One of the four patients in whom this new therapy was tried was a 3-year-old boy found to have acute lymphoblastic leukemia. After the type of therapy was discussed with his parents, his mother agreed to serve as the lymphocyte donor. [Consent form is enclosed.]

She was told of the possible risks to her including early sensitivity reaction to injected bone marrow cells or depletion of the constituents of her own thoracic lymph. Another risk was directly related to the type of surgical procedure that needed to be done, that is, putting a cannula—small tube—into her thoracic duct in her neck.

Later I will comment on the transmitability of leukemia if that is the pleasure of the committee.

Mr. GORE. Let me interrupt there briefly to ask, you did not advise her that there was such a risk?

Dr. VODOPICK. As she alluded to, Dr. Edwards had said this was a very remote possibility. Nonexistent almost. I believe that you will find that in her testimony.

Mr. GORE. All right. Fine.

Dr. **Vodopick.** In order to sensitize her lymphocytes, leukemic cells obtained by bone marrow aspirate from the patient were irridiated with 10,000 roentgens a dose sufficient to kill all these leukemic cells—in other words, these were not live cancer cells—and were injected into several muscle sites of the mother. The patient was then started on conventional chemotherapy consisting of methotrexate and prednisone. It should be emphasized that chemotherapy was begun within 9 days of his first admission to ORAU and was continued for 17 days until his marrow was showed to be hypocellular and evidenced the beginning of a remission on August 23, 1965.

I should comment this is still a usual procedure. You stop the drugs when you have depleted the bone marrow of the leukemic cells. It was then that the lymphocytes via the thoracic duct were obtained from the patient's mother and given intravenously to the patient. No adverse reaction was recorded during this period.

Indeed, the patient's bone marrow did show evidence of remission by September 10, 1965, but this recovery in retrospect was attributed to his chemotherapy rather than to the lymphocyte transfusions although one cannot be absolutely certain about this conclusion. We were all extremely disappointed that 4 months later his leukemia reemerged.

The results of this experimental immunologic approach were published in the medical literature in 1966 and in 1967. The patient was then begun on another course of chemotherapy, consisting of vincristine and prednisone. This first relapse of his leukemia was complicated by a severe staphylococcal infection in his blood stream. When a remission was evident, he was begun on weekly maintenance drug therapy which kept his leukemia under control for 13 months, when another relapse of leukemia and another blood stream staphylococcal infection occurred. Once again, he responded to drug treatment which induced another 8 month remission.

When his leukemia relapsed for the fourth time—and we have records of only four relapses—in November of 1968, the situation was desperate since his leukemia had become refractory to all current antileukemic drugs available. We had only two options—Mrs. Sexton referred to three and perhaps I will go into that later but the two main options were to give only blood transfusions to sustain his life for a few days or weeks longer or try total body irradiation to possibly induce another remission, as I alluded to previously.

Total body irradiation as mentioned previously had induced temporary remission in acute leukemia. After consultation with his mother who was told of the hazards and options, the medical staff chose to give him total-body irradiation. It was not our intent to generate data for the Atomic Energy Commission, or for the National Aeronautics and Space Agency. Our concern and only concern was to keep the patient alive for as long as possible.

Because of his proven propensity to infection, he was taken to a secluded sheltered area—parenthetically this is the patient room in the LETBI facility—after he was irradiated in the METBI facility.

In addition, the principle of reverse isolation was applied in his medical care. In LETBI he could be watched closely via closed circuit television. Initially, a monitoring device—referred to as an umbilicial cord—which recorded his pulse rate and respirations was used to reduce his exposure to hospital personnel, a very potential source of infection. Since the monitoring device which was put around his waist was uncomfortable, it was removed in 1½ hours.

That is the duration of time it was left in place and it was not replaced at any time in the future.

Data were never collected for any reason other than to monitor vital signs as a routine hospital procedure.

Twenty-four days after his radiation exposure in METBI, the patient died with overwhelming staphylococcus aureus and streptococcal infections. These organisms were undoubtedly a part of his own bacterial flora which had become unresponsive to antibiotics and which were unchecked in his body because of his poor immune response. Indeed, he had had two previous blood stream infections with staphylococcus aureau during the course of his illness, both during times of leukemic relapse.

After 1966, as the drug armamentarium became larger and more effective, patients were treated with a combination of drugs and local irradiation or with drugs alone. After this date, all children with acute leukemia at ORAU were started on chemotherapy and continued on maintenance drug therapy.

Two children also received whole brain irradiation which is now an accepted, routine procedure.

Of the 23 children with acute lymphatic leukemia treated at ORINS/ORAU by drug and/or brain irradiation 4 are still living, 14 years, 11 years, and 9 years—2 patients—respectively.

In the present year, 1981, the survival statistics of acute lymphocytic leukemia have improved significantly but still only 50 percent of the children treated are alive at 5 years and only one of two of these children are expected to live beyond 10 years.

In conclusion, a program at ORAU was begun to evaluate the therapeutic effectiveness of total-body irradiation in various hematologic diseases. The administration of this irradiation was given in specially constructed facilities called METBI and LETBI. The results of these studies showed that patients so treated lived as long as those patients treated with drugs and with local irradiation. And this refers more to the fact of the chronic leukemias rather than the acute leukemias.

After analysis of the data, there appeared to be no therapeutic advantage nor disadvantage—life was not shortened—to the total-body irradiation.

Total-body irradiation remains a viable form of therapy in the palliation of a limited number of hematologic diseases. Further studies should be done to assess whether total-body irradiation could complement or potentiate the effectiveness of various drugs now being used.

Mr. Chairman, this concludes my statement.

[The prepared statement of Dr. Vodopick follows:]

STATEMENT BY HELEN VODOPICK, M.D., OAK RIDGE MEDICAL CLINIC

Mr. Chairman and members of the Committee: I am Helen Vodopick, a specialist in Hematology and Medical Oncology in Oak Ridge, TN. From July 1965 to January

1975, I was a member of the Clinical Staff at the ORINS/ORAU Medical and Health Sciences Division.

In order to evaluate the type of treatment given to patients at Oak Ridge Associated Universities (ORAU) we must turn back the calendar to the late 1950's and early 1960's. At that point in time the main modalities of treatment of cancer were surgery, irradiation and very few chemotherapeutic agents. Surgery played the greatest role in the treatment of solid tumors where bulk disease could be removed en masse. However, such an approach most often failed because the tumor had spread beyond the confines of the surgical field. At times radiation was used as a supplement to eradicate residual disease. Unfortunately there were also malignant diseases not amendable to surgery. These diseases were either too widespread in the case of lymphomas (tumor of the lymph glands), and inaccessible to surgery in the case of leukemia. Therefore, it seemed logical to control these latter malignancies with irradiation. A new method was devised to administer this irradiation called total-body irradiation (TBI) whereby the widespread disease would be uniformly treated. The investigation of this treatment method became one of the primary goals of the ORAU Medical Division.

The overall radiation program at ORAU was best described by Dr. Gould Andrews, then Medical Division chairman, in a preface of the 1966 year report of the ORAU Medical Division:

He said, "This is a long range continuing program which has as its objective the improved treatment of disease by means of radiation, both internal and external. Main areas of effort are, (1) the best use of total-body irradiation in the treatment of lymphoma, leukemia and polycythemia; (2) local external irradiation therapy for certain types of cancer, including application of experimental methods based on animal studies * * *."

Since this was a new method of treatment, experimental protocols were developed to evaluate the effectiveness and potential toxicity of this type of irradiation much like protocols now used to assess new drugs in people. Such protocols were reviewed by a human use committee. Lymphomas and chronic leukemias were already known to be sensitive to radiation given in large doses to localized areas. It was still to be determined what the least dose of total-body irradiation administered at various intervals could be used to control these diseases. According to protocol, treatment was titrated to the patient's response. The aim and prime intent of this therapy was to control the lymphoma, leukemia or myeloproliferative disorder.

With this intent, only patients with these diseases were accepted to the Medical Division of ORAU for treatment with TBI. These patients were informed of this experimental approach on their initial admission and were required to sign an admission form attesting to this fact. In addition, the chief of the medical service would again explain the procedure before its actual implementation. Therefore, the patients were fully informed of the type of therapy and the investigational nature of it.

Children with acute leukemia and lymphoma, 19 and 1 cases respectively, were also accepted for TBI treatment. These 20 children treated between 1957 and 1968 were irradiated in the medium exposure TBI unit. The majority of these children had been treated with drugs which failed to arrest their disease.

It must be remembered that between 1965 and 1969 according to American Cancer Society statistics, the one year survival rate for children with acute leukemia under 15 years of age was 40 percent and five year survival rate was 3 percent. The statistics prior to that time were even more dismal. Therefore, it was hoped that by irradiating the whole bone marrow with a high total dose the leukemic cells could be eradicated. Twelve such children were treated in the METBI facility between 1961 and 1968. These children were also treated with chemotherapy. The leukemia was brought under partial control in some cases but re-occurred in all instances. Achieving a remission was possible but maintaining it was not.

Since neither drug therapy nor irradiation had succeeded in curing leukemia in a significant number of children, a new completely different approach was tried. Immunotherapy had worked in animals as proven by Delorme and Alexander. This therapy was based on using a donor's normal sensitized lymphocytes referred to as killer cells, to attack and kill leukemic cells in a recipient. One of the four patients in whom this new therapy was tried was a 3-year-old boy found to have acute lymphoblastic leukemia. After the type of therapy was discussed with his parents, his mother agreed to serve as the lymphocyte donor (consent form is enclosed). She was told of the possible risks to her including early sensitivity reaction to injected bone marrow cells or depletion of the constituents of her own thoracic lymph. Another risk was directly related to the type of surgical procedure that needed to be done, that is, putting a cannula (small tube) into her thoracic duct in her neck. In order to sensitize her lymphocytes, leukemic cells obtained by bone marrow aspirate from the patient were irradiated with 10,000 R, a dose sufficient to kill all these leukemic cells, and were injected into several muscle sites of the mother. The patient was then started on conventional chemotherapy consisting of methotrexate and prednisone. It should be emphasized that chemotherapy was begun within nine days of his first admission to ORAU and was continued for 17 days until his marrow was showed to be hypocellular and evidenced the beginning of a remission on August 23, 1965.

It was then that lymphocytes via the thoracic duct were obtained from the patient's mother and given intravenously to the patient. No adverse reaction was recorded during this period. Indeed the patient's bone marrow did show evidence of remission by September 10, 1965, but this recovery in retrospect was attributed to his chemotherapy rather than to the lymphocyte transfusions although one cannot be absolutely certain about this conclusion. We were all extremely disappointed that four months later his leukemia re-emerged.

The results of this experimental immunologic approach were published in the medical literature in 1966 and in 1967. The patient was then begun on another course of chemotherapy, consisting of vincristine and prednisone. This first relapse of his leukemia was complicated by a severe *Staphylococcal* infection in his blood steam. When a remission was evident, he was begun on weekly maintenance drug therapy which kept his leukemia under control for 13 months, when another relapse of leukemia and another blood stream *Staphylococcal* infection occurred. Once again he responded to drug treatment which induced another eight month remission.

When his leukemia relapsed for the fourth time in November 1968, the situation was desperate since his leukemia had become refractory to all current anti-leukemic drugs available. We had only two options: give only blood transfusions to sustain his life for a few days or weeks longer or try total-body irradiation to possibly induce another remission. Total body irradiation as mentioned previously had induced temporary remission in acute leukemia. After consultation with his mother who was told of the hazards and options, the medical staff chose to give him total-body irradiation. It was not our intent to generate data for the Atomic Energy Commission, or for the National Aeronautics and Space Agency. Our concern and only concern was to keep the patient alive for as long as possible.

Because of his proven propensity to infection, he was taken to a secluded sheltered area after he was irradiated in the METBI facility. In addition the principle of reverse isolation was applied in his medical care. In LETBI he could be watched closely via closed circuit television. Initially a monitoring device referred to as an umbilical cord which recorded his pulse rate and respirations was used to reduce his exposure to hospital personnel, a very potential source of infection. Since the monitoring device which was put around his waist was uncomfortable, it was removed in one and a half hours. Data were never collected for any reason other than to monitor vital signs as a routine hospital procedure.

Twenty-four days after his radiation exposure in METBI, the patient died with overwhelming *Staphylococcus aureus* and *Streptococcal* infections. These organisms were undoubtedly a part of his own bacterial flora which had become unresponsive to antibiotics and which were unchecked in his body because of his poor immune response. Indeed he had had two previous blood stream infections with *Staphylococcus aureus* during the course of his illness, both during times of leukemic relapse.

After 1966, as the drug armamentarium became larger and more effective, patients were treated with a combination of drugs and local irradiation or with drugs alone. After this date, all children with acute leukemia at ORAU were started on chemotherapy and continued on maintenance drug therapy. Two children also received whole brain irradiation which is now an accepted routine accepted procedure. Of the 23 children with acute lymphatic leukemia treated at ORINS/ORAU by drug and/or brain irradiation four are still living, 14 years, 11 years and 9 years (2 patients) respectively.

In the present year, 1981, the survival statistics of acute lymphocytic leukemia have improved significantly but still only 50 percent of the children treated are alive at five years and only one of two of these children are expected to live beyond 10 years.

In conclusion, a program at ORAU was begun to evaluate the therapeutic effectiveness of total-body irradiation in various hematologic diseases. The administration of this irradiation was given in specially constructed facilities called METBI and LETBI. The results of these studies showed that patients so treated lived as long as those patients treated with drugs and with local irradiation. After analysis of the data, there appeared to be no therapeutic advantage nor disadvantage (life was not shortened) to the total-body irradiation. Total-body irradiation remains a viable form of therapy in the palliation of a limited number of hematologic diseases.

Further studies should be done to assess whether total-body irradiation could complement or potentiate the effectiveness of various drugs now being used.

Mr. Chairman, this concludes my statement.

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES
MEDICAL DIVISION

PATIENT ADMITTANCE AGREEMENT

In consideration of my being accepted and admitted to the Research Hospital operated by the Oak Ridge Institute of Nuclear Studies, I, on behalf of myself, my heirs, executors, administrators, and assigns, convenant, understand and agree as follows:

1. To hereby release and discharge the Oak Ridge Institute of Nuclear Studies, its officers, agents, and employees from any actions, damages or claims resulting from my hospitalization in said hospital and/or any treatments and care received while in said hospital or by reason of my having been a patient therein.

2. That any treatments administered to me may be experimental.

3. That I have not been influenced in making this agreement by any representations or statements regarding improvement in my physical condition or the probable results of any treatments received, but instead expressly assume all risks incident to my hospitalization, care and treatment.

4. I understand that but for this agreement on my part, I would not be accepted and admitted as a patient in said hospital.

5. I covenant that I have carefully read the foregoing and fully understand the meaning and contents thereof, and have executed the same of my own free will and choice.

Date [illegible] 1965

Signed [illegible]
Patient [illegible] years

WITNESSES:

[illegible]

[illegible]

[illegible]
Father or Guardian

[illegible]
Mother

DATE :

lymph and inject this material in her boy, expecting an immunological response from the parent's possibly formed anti-leukemic antibodies.

8.2 65 The pt's mother has accepted to go ahead with the procedure. She will be hospitalized and worked up. He has developed an ecchymotic area at the site of IV injection on right elbow flexure. No other areas of ecchymosis or petechiae. Asymptomatic, though c̄ poor appetite.

8.4-65 Pt in good condition. His mother received bone marrow aspiration today by Dr. Velazquez. He will have bone marrow aspiration tomorrow under general anesthesia, taken from posterior iliac & probably proximal tibia. This marrow will be irradiated & given later to his mother.

Sexton, Dwayne
PATIENT'S NAME

J11670
HOSP. NO.

PROGRESS NOTE

Abdomen (cont): normal consistency. The spleen is not palpable. The bowel sounds are normal. There is no other organomegaly or masses palpable.

Genital and Rectal: Normal external genitalia for this age. Circumcised penis. Rectal examination negative.

Extremities: There is an area of ecchymosis on the left ankle as noted previously. There is a mild bruise in his right knee, with some excoriations There is no swelling or pain in the joints.

Neurological: Deep tendon reflexes are normal bilaterally. Abdominal cutaneous and cremasteric reflexes present and normal. No abnormal reflexes elicited.

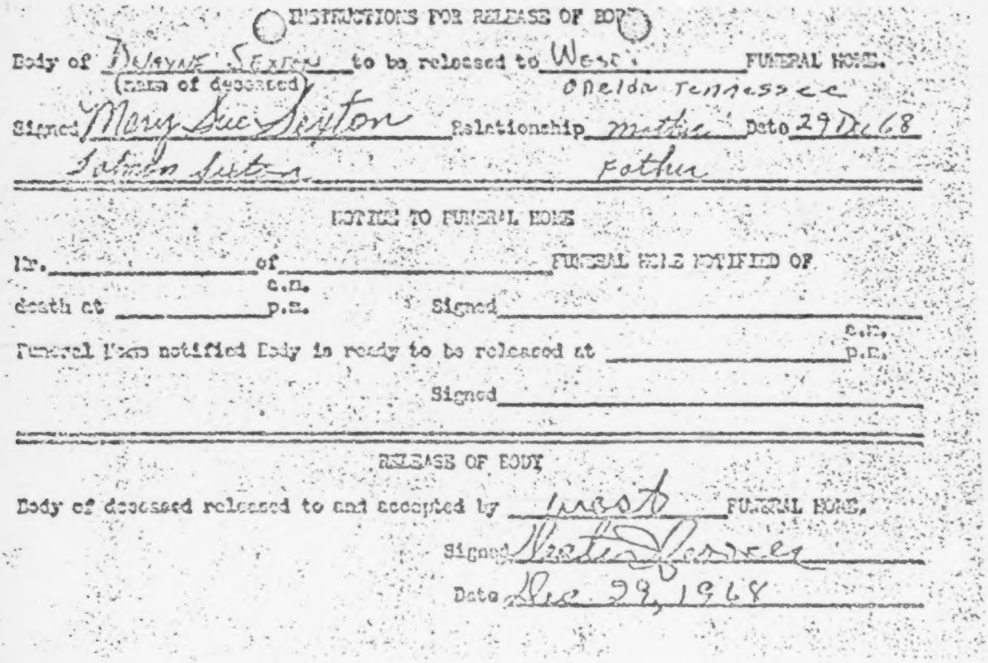
Lymphatics: There is lymph node enlargement present in both axillary and inguinal areas. The size of the former varies from 0.5 to 1.0 cm and the latter are very small, approximately 0.5 cm. They are firm in consistency, nontender, movable, and there are no changes present of the overlying skin.

On admission, this patient was seen by Dr. Edwards and Dr. Vodopick. A bone marrow aspiration was done and the diagnosis of acute lymphoblastic leukemia was made. The plan for this child is to start treatment with one of the conventional therapeutic means and then attempt bone marrow injection from him to his parents, to perform later transfusion of lymph from the parents' thoracic duct into his blood stream.

Impression: Acute lymphoblastic leukemia.

J Ahumada
J. Ahumada, M.D.
C L Edwards

/voh



INSTRUCTIONS FOR RELEASE OF BODY

Body of Dewayne Sexton (name of deceased) to be released to West FUNERAL HOME.
Oneida Tennessee

Signed Mary Sue Sexton Relationship mother Date 29 Dec 68

Solomon Sexton Father

NOTICE TO FUNERAL HOME

Mr. ____________ of ____________ FUNERAL HOME NOTIFIED OF

death at ____________ a.m. p.m. Signed ____________

Funeral Home notified Body is ready to be released at ____________ a.m. p.m.

Signed ____________

RELEASE OF BODY

Body of deceased released to and accepted by West FUNERAL HOME.

Signed ____________

Date Dec 29, 1968

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES
Oak Ridge, Tennessee

Request for Autopsy

NAME OF DECEASED Dwayne Sexton ROOM

BED NO. HOSPITAL CASE NO. 511670 AGE 6 SEX Male

MARITAL STATUS OF DECEASED IS: (Encircle word that applies)

[✓ SINGLE] MARRIED WIDOWED SEPARATED (but not divorced) DIVORCED

TIME OF DEATH Dec 29 1968 0100
Month Day Year Hour

1. I hereby certify that I assume custody of the body of the above-designated deceased for purpose of burial, and assume responsibilities connected therewith.

2. I hereby authorize the Pathologist of the Oak Ridge Institute of Nuclear Studies and such person or persons as he may designate to perform an autopsy on the body of my Son
(State relationship of deceased to signer.)

I authorize him, too, to have present at that autopsy such persons as he may deem proper.

3. The autopsy here authorized may be either a complete or partial autopsy. Such organs and tissues may be removed as the physician performing the autopsy considers necessary for study subsequent to the autopsy, to accomplish the purposes of the autopsy, to eliminate undesirable radioactivity, or for therapeutic purposes. (If the nature and extent of this autopsy or the right to remove parts of the body are to be limited in any way, those LIMITATIONS SHOULD BE CLEARLY STATED BELOW). In the absence of any stated limitations, it is to be understood that the pathologist by whom the operation is performed is to be the sole judge of the nature and extent of the autopsy. He is specifically authorized to examine the cranial contents and the femur, if such examination is necessary to complete study of the case.

LIMITATIONS (Specify): Limited to chest + abdomen with organs replaced after examination

4. After the autopsy, the body should be released to: Wests Funeral Home
Oneida, Tenn

5. I FURTHER CERTIFY THAT I HAVE READ AND UNDERSTAND ALL THE FOREGOING.

DATE 29 Dec 68 SIGNATURE Salmon Sexton

ADDRESS 3625 Memorial Blvd.
Kingsport, Tennessee

WITNESSES: 1. Hem K Spurlock 2.

Revision of March 1957.
Med. 0139

ORAU Path # 9254

We understand and agree to a special experimental procedure designed to try to help our child who has acute leukemia. This will consist of removing bone marrow from the child, subjecting the marrow to radiation designed to kill the leukemic cells, and subsequently injecting these cells into the mother. At a later date it is planned to operate on the mother to drain lymph from the thoracic duct to obtain cells that can be injected back into the patient in an effort to combat the leukemia.

Since this is a new and experimental procedure, there are some risks involved for both mother and child. The nature of these has been explained to us and we are willing to accept them.

Our acceptance of this procedure is entirely voluntary. The staff of the Medical Division has put no pressure on us to agree to this, and has freely offered more conventional treatment as an alternative.

Talmon Sexton

Mary Sue Sexton

8-5-65

Date

Mildred V. Houts, R.N.

Witness

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES
MEDICAL DIVISION
OAK RIDGE, TENNESSEE

AUTHORITY TO OPERATE

(If competent, patient should sign in space indicated. If a minor or incapable of signing, representatives should sign in lower spaces.)

DATE Aug

THIS IS TO CERTIFY THAT I ☐ WE ☒ THE UNDERSIGNED, CONSENT TO THE ADMINISTRATION OF WHATEVER ANESTHETICS AND THE PERFORMING OF WHATEVER OPERATION, IN THE OPINION OF THE MEDICAL STAFF, MAY BE NECESSARY OR ADVISABLE.

Talmon Dwayne Sexton
NAME ADDRESS

EXCEPTIONS, IF ANY

WITNESS SIGNATURE OF PATIENT

PATIENT IS A MINOR ✓, OR STATE WHY INCAPABLE OF SIGNING

Mary E. Smithey — R.N.

SIGNATURE Mary Sue Sexton (mother)

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES
MEDICAL DIVISION
OAK RIDGE, TENNESSEE

AUTHORITY TO OPERATE

(If competent, patient should sign in space indicated. If a minor or incapable of signing, representatives should sign in lower spaces.)

DATE 8-22-65

THIS IS TO CERTIFY THAT I ☐ WE ☒ THE UNDERSIGNED, CONSENT TO THE ADMINISTRATION OF WHATEVER ANESTHETICS AND THE PERFORMING OF WHATEVER OPERATION, IN THE OPINION OF THE MEDICAL STAFF, MAY BE NECESSARY OR ADVISABLE.

Dwayne Sexton
NAME ADDRESS

EXCEPTIONS, IF ANY

WITNESS M. Mackley R.N. SIGNATURE OF PATIENT
[illegible]

PATIENT IS A MINOR Yes, OR STATE WHY INCAPABLE OF SIGNING Mary Sue Sexton
Parents Talmon Sexton

SIGNATURE

SEXTON, DWAYNE

OAK RIDGE ASSOCIATED UNIVERSITIES
27 11 67 Oak Ridge, Tennessee

Patient Admittance Agreement

The Oak Ridge Institute of Nuclear Studies (ORINS) Medical Research Hospital is operated by Oak Ridge Associated Universities (ORAU) for the U. S. Atomic Energy Commission (AEC) for the conduct of certain clinical research programs. These programs are mainly in areas allied to the application of radiation and radioisotopes to medicine and other health sciences.

I understand that I have been accepted as a patient for admission to the hospital, or as an outpatient, because my physical condition has been determined by the hospital staff to make me a suitable patient for a currently active clinical research project.

I further understand that while a patient at the research hospital examinations, treatments, and tests may be prescribed which are experimental in nature and I hereby consent to such examinations, treatments, or tests. Notwithstanding the above, I reserve the right to a full explanation of any such proposed examination, test, or treatment and the right to withdraw my consent. I further reserve the right to withdraw completely should I find that I am unable to continue.

I further understand that I can remain in the research hospital only so long as I am needed for research purposes, and that I must be discharged when my participation in a study is completed and when, in the opinion of the hospital staff, my medical condition permits. In such event, I understand that ORAU, its officers, employees, and agents, cannot assume responsibility for any continued medical care.

The above statements have been explained to me by the member of the Medical Division staff named below. I understand and accept the statements.

I have not been influenced in making this agreement by any representations or statements regarding improvement in my physical condition or the probable results of any treatments received, but instead expressly assume all risks incident to my hospitalization, care, and treatment.

Patient's signature	Medical Division staff member's signature
Parent or guardian's signature	Date

PATIENT ADMITTANCE AGREEMENT MED-13(2-67)

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Patient Admittance Agreement

The Oak Ridge Institute of Nuclear Studies (ORINS) Medical Research Hospital is operated by Oak Ridge Associated Universities (ORAU) for the U. S. Atomic Energy Commission (AEC) for the conduct of certain clinical research programs. These programs are mainly in areas allied to the application of radiation and radioisotopes to medicine and other health sciences.

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The above statements have been explained to me by the member of the Medical Division staff named below. I understand and accept the statements.

I have not been influenced in making this agreement by any representations or statements regarding improvement in my physical condition or the probable results of any treatments received, but instead expressly assume all risks incident to my hospitalization, care, and treatment.

Mrs. Talmer Sexton (mother)	Pete M. Hatt
Patient's signature	Medical Division staff member's signature
	24 Nov. 67
Parent or guardian's signature	Date

PATIENT ADMITTANCE AGREEMENT MED-13(2-67)

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

I authorize the performance upon Dwayne Sexton
(myself or name of patient)
of the following treatment: Total Body Irradiation

(State nature of treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may be unpredictable.

DATE: 3 Dec '68 x Mary Sue Sexton
(Patient or person authorized to consent for patient)

WITNESS:

I have talked with Mary Sue Sexton about
Name
the proposed course of treatment to be given Dwayne Sexton
Name
including the following:* purpose and alternatives of therapy & probable effect

C. L. Edwards 3 Dec. '68
Physician Date

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

CONSENT TO EXPERIMENTAL TREATMENT MED-146(2-67)

Mr. GORE. Thank you very much, doctor.

Dr. Frank Comas, chief of the department of radiation oncology at the University of Tennessee Memorial Hospital.

Welcome, doctor.

Dr. COMAS. Mr. Chairman and members of the committee, my name is Frank Comas. I am chief of the department of radiation oncology at the University of Tennessee Memorial Hospital.

I was associated with the Oak Ridge Institute of Nuclear Studies, later Oak Ridge Associated Universities, between 1958 and 1969. One of my activities was supervising the treatment of patients who were given total body irradiation.

In the course of those studies data was gathered on the side effects of total body irradiation, and some of that information was made available to NASA. It has been alleged that it was the purpose of our studies to generate data for NASA, but this is not true.

The total body irradiation program started well before NASA came into the scene, and it continued for several years beyond the termination date for data collection for NASA.

The purpose of our studies was to define the role of total body irradiation in two different settings. One was the heroic use of rather large doses of radiation in the treatment of acute leukemia in children. In those years, that was a fatal disease, and much experimental work had been done to the effect that maybe the disease could be treated by wiping out the leukemic cells with radiation.

I do not consider myself an expert in this field and will comment no further on the merits of this approach. I did not make the decisions whether to irradiate or not, but I did administer the actual radiation treatment in almost all patients that were so treated, and I felt justified in doing so when nothing else appeared to be of much value.

The other much larger group of patients were those with chronic leukemias and disseminated lymphomas. These are diseases which follow a more chronic course, sometimes with possibility of survival for several years. Here, the object of the treatment was to prolong life, and make it as comfortable as possible.

Those patients were treated with total body irradiation exposures of 50 to 100 R which is a moderate amount of total body irradiation, with hardly any danger to life from the treatment itself, and usually with rather mild side effects.

Our efforts met with limited success. We did not salvage a single child with acute leukemia given total body irradiation. We obtained a few short remissions, but cures did not appear until the state of the art had improved the effective combination of drugs around 1970. By then, my colleagues were doing very well without any radiation in some types of acute leukemia. Even before then, our overall results compared favorably to the national experience.

Appended in the back is figure 1. It is the upper two panels that are relevant to this statement.

With the other group we obtained lots of partial remissions; and a few complete remissions. That is when the disease appears to disappear but comes back after a period of time. In terms of a phase I study—which tests for tolerance by the patient—the treatment went well without significant toxicity.

In terms of a phase II study—when one test for how effective that treatment may be—I only know that it worked but cannot say how well because that data has not been analyzed for survival and remission induction, other than for patients with chronic myeloid leukemia.

In terms of a phase III study, we never intended to compare total body irradiation versus another form of treatment. We did not have the number of patients to do such a study.

If we look from the perceptives of the 1980's to our efforts to the 1960's this is what I find. Total body irradiation for acute leukemia is still being tried in an experimental way but with radiation doses much larger than those we used.

Total body irradiation for lymphomas is now much more prevalent than it was during my years at ORAU. It is given nowadays in fractionated rather than single doses, and in much larger amounts than we did then. In retrospect we did not dare enough. But, then, we were exploring new frontiers, and it was the feeling of our group the first thing was not to harm.

Mr. Chairman, this concludes my statement.

[The prepared statement of Dr. Comas follows:]

STATEMENT OF FRANK V. COMAS, M.D., CHIEF, DEPARTMENT OF RADIATION ONCOLOGY, UNIVERSITY OF TENNESSEE MEMORIAL HOSPITAL

Mr. Chairman and members of the Committee, my name is Frank Comas. I am Chief of the Department of Radiation Oncology at the University of Tennessee Memorial Hospital.

I was associated with the Oak Ridge Institute of Nuclear Studies, later Oak Ridge Associated Universities, between 1958 and 1969. One of my activities was supervising the treatment of patients who were given total body irradiation.

In the course of those studies data was gathered on the side effects of total body irradiation, and some of that information was made available to NASA. It has been alleged that it was the purpose of our studies to generate data for NASA, but this is not true. The total body irradiation program started well before NASA came into the scene, and it continued for several years beyond the termination date for data collection for NASA.

The purpose of our studies was to define the role of total body irradiation in two different settings. One was the heroic use of rather large doses of radiation in the treatment of acute leukemia in children. In those years that was a fatal disease, and much experimental work had been done to the effect that maybe the disease could be treated by wiping out the leukemic cells with radiation. I do not consider myself an expert in this field and will comment no further on the merits of this approach. I did not make the decisions whether to irradiate or not, but I did administer the actual radiation treatment in almost all patients that were so treated, and I felt justified in doing so when nothing else appeared to be of much value.

The other much larger group of patients were those with chronic leukemias and disseminated lymphomas. These are diseases which follow a more chronic course, sometimes with possibility of survival for several years. Here, the object of the treatment was to prolong life, and make it as comfortable as possible. Those patients were treated with total body irradiation exposures of 50 to 100 R which is a moderate amount of total body irradiation, with hardly any danger to life from the treatment itself, and usually with rather mild side effects.

Our efforts met with limited success. We did not salvage a single child with acute leukemia given total body irradiation. We obtained a few short remissions, but cures did not appear until the state of the art had improved to effective combination of drugs around 1970. By then, my colleagues were doing very well without any radiation in some types of acute leukemia. Even before then, our overall results compared favorably to the national experience.

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In terms of a phase II study—when one tests for how effective that treatment may be—I only know that it worked but cannot say how well because that data has not been analyzed for survival and remission induction, other than for patients with chronic myeloid leukemia.

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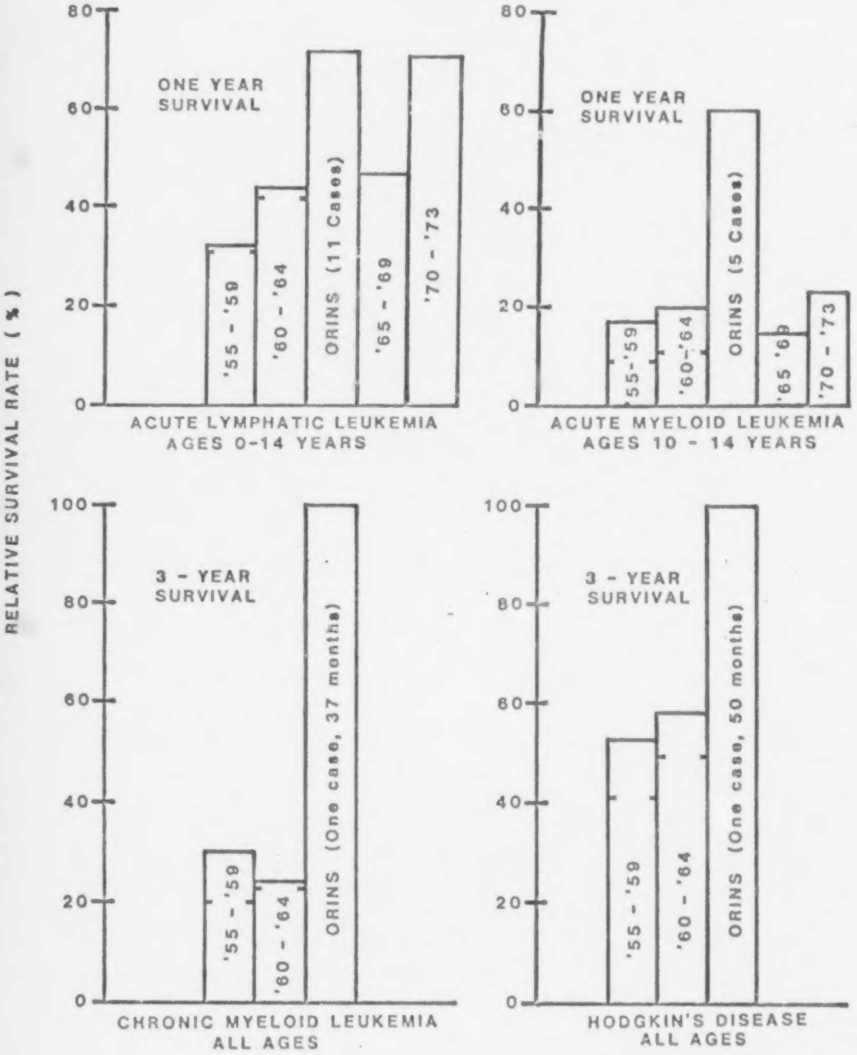
If we look from the perceptives of the 1980s to our efforts of the 1960s this is what I find. Total body irradiation for acute leukemia is still being tried in an experimental way but with radiation doses much larger than those we used. Total body irradiation for lymphomas is now much more prevalent than it was during my years at ORAU. It is given nowadays in fractionated rather than single doses, and in much larger amounts than we did then. In retrospect we did not dare enough. But, then, we were exploring new frontiers, and it was the feeling of our group the first thing was not to harm.

Mr. Chairman, this concludes my statement.

END RESULTS IN CANCER (US DHEW) IN OVER 100 U. S. HOSPITALS AND ORINS

Relative Survival Rates by Calendar Periods of Diagnosis



ORINS cases treated with TBI and chemotherapy

Fig. 1

Mr. GORE. Thank you very much.

We would like to now hear from Dr. Karl Hubner, chief of outpatient nuclear medicine and director of the Radiation Emergency Assistance Center training site at ORAU.

I would like to make two brief comments.

First, shortly after you get started I am afraid I will have to interrupt your testimony. We have a significant, important vote on the floor for which I will have to go over. But second, I would like to take this occasion in the record to congratulate your son who is being sworn in as a citizen of the United States today, as this subcommittee meets, and this is some personal sacrifice for you to be here in spite of that occasion, but it is a happy one and I wanted to note it in the record.

Since those are the second bells and this is an appropriate breaking point, we will recess just for about 8 or 10 minutes and when we come back we will hear from you.

[Brief recess.]

Mr. GORE. The subcommittee will come back to order.

We were just about to hear from Dr. Karl Hubner.

Dr. HUBNER. Thank you, Mr. Chairman. I appreciate the opportunity to present to the committee the results of my detailed review of the evolution of the consent form for human subjects and the ORINS/ORAU Medical Division compliance with the intent of informed consent.

The 1947 Nuremberg Code of Ethics established fundamental principles for scientists and physicians involved in finding new or improved treatments for human diseases or new insights into the basic mechanisms of diseases which would help develop new avenues for treatment or eradication of certain diseases.

In this code of professional medical ethics, the respect for the human rights of the patient and his/her safety from undue physical or psychological harm is the paramount consideration.

Point 1 of the Nuremberg Code states: "The voluntary consent of the human subject is essential." The code also covers the "legal capacity" of persons, free power of choice, and ability to make value judgment. Assurance of the consent would rest upon the individual directing the experiment.

When the ORINS Medical Division began admitting patients in 1950, a special application form for admission had to be signed by the patient or his legal guardian in order to be admitted to the clinical research program. This early patient admittance agreement spelled out some of the essential statements required for today's (1981) consent forms: The treatment may be experimental, the patient is given no promises regarding improvement of his physical condition, there may be certain risks involved in the experimental treatment, the patient may refuse to participate as a patient in the hospital, and the patient understands the agreement and participates of his/her own free will and choice. A copy of this consent form is included as appendix A.

In 1957, the ORINS Medical Division initiated consent forms for special procedures. These forms were tailored to the cases and procedure concerned and were used in addition to the general admittance agreement which was also revised in 1957. A copy of each is attached as appendix B.

For patients scheduled for total body irradiation, the chief of clinical services of the ORINS Medical Division would discuss with the patient or their legal guardians the nature of the procedure, the amount of TBI, the possible risks, and would obtain a signed consent form.

In 1964, the Declaration of Helsinki emphasized that clinical research should be: one, based on laboratory and animal experiments or other scientifically established facts, two, conducted by scientifically qualified persons under the supervision of a qualified medical person, three, preceded by careful assessment of inherent risks versus benefits, and four, done only with full information to the patient and with free consent.

The Helsinki document differentiated between clinical research in which the aim is therapeutic for the patient and the purely scientific aim without benefit to the patient subject to the research.

In November 1966, the American Medical Association [AMA] adopted the ethical principles of the Declaration of Helsinki to aid physicians to fulfilling their responsibilities while engaged in clinical investigations of new drugs and procedures.

According to the AMA's guidelines, consent is only attained after disclosure of an investigative new drug or experimental procedure, explanation of the risks involved, indication of possible therapeutic benefits, discussion of alternate drugs or procedures, an offer to answer any questions, and the signing of a consent by the patient.

In late 1966, Dr. Gould Andrews decided to revise and formalize a code of ethics for human experimentation for the ORAU Medical Division. In early 1967, with the assistance of Dr. Heyssel of Vanderbilt University and Dr. Lange of the University of Tennessee, ORAU drafted guidelines for a human use committee, developed new consent forms, and officially formed a human use committee. In 1969, ORAU's "statement of assurance" was accepted by the U.S. Department of Health, Education, and Welfare. Appendix C contains the 1967 guidelines, revised consent forms, and human use committee membership.

Subsequently, OARU was, and still is, included in the cumulative list of organizations and institutions in compliance with DHEW policy and regulations on protection of human subjects.

In reviewing the ORINS/ORAU Medical Division consent forms used over the years, I believe them to be fully consistent with reasonable medical practice during the time period.

My review also indicated that the choice of therapy in the ORINS/ORAU clinical program was dictated by the potential benefit the therapy offered the patient. In a paper published in 1950, Dr. Andrews stated, "The welfare of the patients takes precedence over every other consideration." I believe that guiding principle has continued ever since.

That concludes my statement, Mr. Chairman. I will be pleased to answer questions.

[The prepared statement of Dr. Hübner follows:]

STATEMENT BY KARL F. HÜBNER, M.D., CHIEF, OUTPATIENT NUCLEAR MEDICINE, DIRECTOR, RADIATION EMERGENCY ASSISTANCE CENTER/TRAINING SITE, OAK RIDGE ASSOCIATED UNIVERSITIES

Mr. Chairman and members of the Committee, my name is Karl Hübner and I am currently the Director of the Radiation Emergency Assistance Center and Training Site and Chief of the Clinical Nuclear Medicine Program at the Medical and Health Sciences Division of Oak Ridge Associated Universities.

I appreciate the opportunity to present the Committee with the results of my detailed review of the evolution of the Consent Forms for human subjects and the ORINS/ORAU Medical Division compliance with the intent of informed consent.

The 1947 Nuremberg Code of Ethics established fundamental principles for scientists and physicians involved in finding new or improved treatments for human diseases or new insights into the basic mechanisms of diseases which would help develop new avenues for treatment or eradication of certain diseases. In this code of professional medical ethics, the respect for the human rights of the patient and his/her safety from undue physical or psychological harm is the paramount consideration.

Point One of the Nuremberg Code states: "The voluntary consent of the human subject is essential." The code also covers the "legal capacity" of persons, free power of choice and ability to make value judgment. Assurance of the consent would rest upon the individual directing the experiment.

When the ORINS Medical Division began admitting patients in 1950, a special application form for admission had to be signed by the patient or his legal guardian in order to be admitted to the clinical research program. This early patient admittance agreement spelled out some of the essential statements required for today's (1981) consent forms: the treatment may be experimental, the patient is given no promises regarding improvement of his physical condition, there may be certain risks involved in the experimental treatment, the patient may refuse to participate as a patient in the hospital, and the patient understands the agreement and participates of his/her own free will and choice. A copy of this consent form is included as Appendix A.

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In late 1966, Dr. Gould Andrews decided to revise and formalize a Code of Ethics for Human Experimentation for the ORAU Medical Division. In early 1967 with the assistance of Dr. Heyssel of Vanderbilt University and Dr. Lange of the University of Tennessee, ORAU drafted guidelines for a Human Use Committee, developed new consent forms and officially formed a Human Use Committee. In 1969, ORAU's "statement of assurance" was accepted by the U.S. Department of Health, Education and Welfare. Appendix C contains the 1967 guidelines, revised consent forms and Human Use Committee membership. Subsequently, ORAU was, and still is, included in the Cumulative List of Organizations and Institutions in Compliance with DHEW Policy and Regulations on Protection of Human Subjects.

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My review also indicated that the choice of therapy in the ORINS/ORAU clinical program was dictated by the potential benefit the therapy offered the patient. In a paper[1] published in 1950, Dr. Andrews stated, "The Welfare of the patients takes precedence over every other consideration." I believe that guiding principle has continued ever since.

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[1] "Southern Surgeon," v. 16, pp. 577-583, 1950.

That concludes my statement Mr. Chairman. I will be pleased to answer questions.

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES
Oak Ridge, Tennessee

APPLICATION FOR ADMISSION TO THE MEDICAL DIVISION HOSPITAL

The Oak Ridge Institute of Nuclear Studies, Medical Division, has a 30-bed hospital unit as a part of its research facilities in Oak Ridge. The purpose of the hospital is to seek and develop new methods of diagnosis and treatment and to study fundamental problems of certain diseases in the hope that the information obtained can be used for the practical treatment of these diseases and the benefit of patients. The hospital, which is staffed by qualified physicians and nurses, is especially designed for the use of radioactive isotopes. Because of the nature of the facilities, only certain types of diseases can be studies and treated.

The applicant recognises the right of the hospital to determine the eligibility of all persons for admission as well as the right to refuse admission to any applicant. Moreover, the hospital reserves the right to discharge the patient at such time as it deems advisable.

No charge is made for hospitalisation and treatment in the research hospital. The hospital endeavors to provide the most complete care for the patient and the patient's welfare is the primary concern of the hospital. No treatments are employed except those which the hospital feels will benefit the patient. However, the applicant must understand and appreciate the fact that some of the treatments used and that will be used are new, are based upon experiments on animals and that the degree of probable benefit, if any, cannot always be predicted in advance. The applicant is expected to fully cooperate at all times with the hospital and its staff. The applicant hereby grants permission for such operations, and biopsies as are deemed necessary and advisable by the hospital. It is agreed that the hospital may make photographs of treatments, procedures, operations, etc. which are performed upon the patients while in the hospital and use the same in scientific publications. At the time of admission to the hospital the applicant will be required to sign such further entrance agreements as may be required by the Institute and at all times comply with the rules and regulations of the hospital.

On the basis of the foregoing, admission to said hospital is requested by ______________________.

This May 15 ____________ day of ________, 1950

Mrs. C. A. L.
Applicant

witness – [illegible] M.D.

WITNESS:
[illegible] M.D.

____

This application should be submitted to the nearest participating medical school listed in the patient information pamphlet. It should not be sent directly to Oak Ridge.

APPROVED BY:
[illegible] M.D.
Member [illegible] Committee - U. of Tenn. Hospital
Title

______________________ Medical School

No CH-001

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES

WAIVER AND RELEASE

In consideration of my being selected, accepted and admitted as a patient in the research hospital conducted and operated by the Oak Ridge Institute of Nuclear Studies, a nonprofit corporation, at Oak Ridge, Tennessee, for hospitalization and the receiving of medical treatment, attention and care by experimental methods and means and/or otherwise, I, Mrs. C. A. ____________________, for myself, my heirs, executors, administrators and assigns, do hereby release, acquit and forever discharge said Oak Ridge Institute of Nuclear Studies, its officers, physicians, nurses, agents, servants and employees, their heirs, successors and assigns, and each of them, of and from any and all actions, causes of action, claims, demands, damages, loss, costs and expenses, whether direct or consequential, arising or claimed to arise because of or as the result of my said hospitalization in said hospital and/or any treatments and care while a patient in said hospital or by reason of my having been a patient therein.

I acknowledge that I have been fully advised by the Oak Ridge Institute of Nuclear Studies concerning the character and kind of treatment and care which I will receive as such patient and I understand that for the most part, they will be experiments with no definite promise of improvement in my physical condition. Notwithstanding such fact, I have executed this agreement for the purposes herein contained of my own free will and choice. I covenant that I have not been influenced to any extent whatever in making this release by any representations or statements regarding my physical condition or the probable results of any treatments therefor, and I hereby expressly assume all risks thereof.

I further understand that but for this agreement on my part, I would not be accepted by the Oak Ridge Institute of Nuclear Studies as a patient in its said hospital.

I covenant that I have carefully read the foregoing and know the contents thereof.

IN WITNESS WHEREOF, I have hereunto set my hand on the [illegible] day of May, 19[illegible].

Mrs. C. A. L

ATTEST:

[illegible]

J. Edward Sherman

Father or Guardian

Mother

STATE OF TENNESSEE)
)
COUNTY OF Anderson)

Personally appeared before me, Mary E. Russell, a Notary Public in and for the State and County aforesaid, the within named bargainor, Mrs. C. A. L, with whom I am personally acquainted, and who acknowledged that he executed the foregoing instrument for the purposes therein contained.

WITNESS my hand and official seal in Anderson County, Tennessee of this, the 4th day of May, 19[illegible].

Mary E. Russell
Notary Public

My notarial commission expires: ____________.

We are signing this statement to indicate our understanding and approval of the special treatment planned for our son,

1. We realize that he is seriously ill with acute leukemia and that the outlook for him is extremely poor under any circumstances. We are willing to have him given a special experimental form of treatment consisting of total body irradiation in a dose that is much larger than that used ordinarily, to be followed by transfusion of bone marrow. We understand that there is a serious risk in this treatment.

Signed: [redacted]

[redacted]

Attest:

Mary E. Sutley

Dated this 25 day of Mar 1957.

No. [illegible]

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES

Oak Ridge, Tennessee

APPLICATION FOR ADMISSION TO THE MEDICAL DIVISION HOSPITAL

The Oak Ridge Institute of Nuclear Studies, Medical Division, has a 30-bed hospital unit as a part of its research facilities in Oak Ridge. The purpose of the hospital is to seek and develop new methods of diagnosis and treatment and to study fundamental problems of certain diseases in the hope that the information obtained can be used for the practical treatment of these diseases and the benefit of patients. The hospital, which is staffed by qualified physicians and nurses, is especially designed for the use of radioactive isotopes. Because of the nature of the facilities, only certain types of diseases can be studied and treated.

The applicant recognizes the right of the hospital to determine the eligibility of all persons for admission as well as the right to refuse admission to any applicant. Moreover, the hospital reserves the right to discharge the patient at such time as it deems advisable.

No charge is made for hospitalization and treatment in the research hospital. The hospital endeavors to provide the most complete care for the patient and the patient's welfare is the primary concern of the hospital. However, the applicant must understand and appreciate the fact that some of the treatments that will be used are new, are based upon experiments on animals and that the degree of probable benefit, if any, cannot always be predicted in advance. The applicant is expected to fully cooperate at all times with the hospital and its staff. The applicant hereby grants permission for such operations, and biopsies as are deemed necessary and advisable by the hospital. It is agreed that the hospital may make photographs of the applicant and his or her treatments, procedures, operations, etc., which are performed upon the patients while in the hospital and use the same in scientific publications. At the time of admission to the hospital the applicant will be required to sign such further entrance agreements as may be required by the Institute and at all times comply with the rules and regulations of the hospital.

On the basis of the foregoing, admission to said hospital is requested by [illegible]

This [illegible] day of [illegible] 19[illegible].

WITNESS:

[illegible] Edwards

[illegible]

Applicant [illegible]

[illegible]
Father or Guardian

Mrs. [illegible]
Mother

This application should be submitted to the nearest participating medical school listed in the patient information pamphlet. It should not be sent directly to Oak Ridge.

APPROVED BY:

____

____
Title

ACCEPTED BY:

____

____
Title

______________________ Medical School

No. ______

OAK RIDGE INSTITUTE OF NUCLEAR STUDIES

WAIVER AND RELEASE

In consideration of my being selected, accepted and admitted as a patient in the research hospital conducted and operated by the Oak Ridge Institute of Nuclear Studies, a nonprofit corporation, at Oak Ridge, Tennessee, for hospitalization and the receiving of medical treatment, attention and care by experimental methods and means and/or otherwise, I, ______________, for myself, my heirs, executors, administrators and assigns, do hereby release, acquit and forever discharge said Oak Ridge Institute of Nuclear Studies, its officers, physicians, nurses, agents, servants and employees, their heirs, successors and assigns, and each of them, of and from any and all actions, causes of action, claims, demands, damages, loss, costs and expenses, whether direct or consequential, arising or claimed to arise because of or as the result of my said hospitalization in said hospital and/or any treatments and care while a patient in said hospital or by reason of my having been a patient therein.

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I further understand that but for this agreement on my part, I would not be accepted by the Oak Ridge Institute of Nuclear Studies as a patient in its said hospital.

I covenant that I have carefully read the foregoing and know the contents thereof.

IN WITNESS WHEREOF, I have hereunto set my hand on the ____ day of ________, 19__.

____
Applicant

L. C. A______
Father or Guardian

Mae E. ______
Mother

ATTEST

Billy Edwards
____

STATE OF TENNESSEE

COUNTY OF

Personally appeared before me, ______________ a Notary Public in and for the State and County aforesaid, the within named bargainor, ______________, with whom I am personally acquainted, and who acknowledged that he executed the foregoing instrument for the purposes therein contained.

WITNESS my hand and official seal in ______________ County, Tennessee of this, the ______ day of ______________, 19___.

____
Notary Public

My notarial commission expires ______________.

AEC Oak Ridge, Tenn.

Report of Meeting to Consider Establishment of Committee on Human Use

April 6, 1967

Present: Dr. Robert Heyssel, Dr. Robert Lange, Dr. Lowell Edwards, and
Dr. Gould Andrews

A meeting was held at the Medical Division on April 6, 1967, to discuss the establishment of a committee on clinical investigation which would serve to advise and monitor the Medical Division program in relation to the ethics of research in human beings and the suitability, from this viewpoint, of research going on at the Medical Division. It was pointed out that this committee would be a replacement for more informal arrangements that had previously existed in the Medical Division. The desire to have two outside consultants - Dr. Lange and Dr. Heyssel - had been stimulated by a suggestion from the Atomic Energy Commission which followed the meeting of their Advisory Committee in November, 1966. It had been pointed out by the Advisory Committee and the Commission that they did not wish to imply any criticism of our past practices, but that because of the widespread concern over ethics of human experimentation, and the possibility that some criticism, either valid or not, might arise, they believed it would be desirable to have some outside, disinterested consultants who were familiar with what we were doing, and who had passed on each individual research proposal.

A rather general discussion was held. We considered at some length the function of the committee. It was our opinion that the committee would serve to review research proposals and decide whether or not they were justifiable from the viewpoint of any risk that might be involved in studies done on human beings. If no risk is involved, the committee would not make any effort to evaluate the research proposal from the point of view of its scientific value. However, if there are significant hazards, the committee would need to evaluate the scientific merit of the proposal and balance it against the possible risks.

Name of the Committee

We chose the title, "Committee on Human Studies."

a. Composition of the Committee

It was decided to have, in addition to Dr. Lange and Dr. Heyssel, three members of the Medical Division staff on the committee. These would probably include one Ph.D. and two M.D.s. Andrews would be one of the Medical Division members and Edwards would sit in on the meetings without being an active member of the committee. We discussed at some length the fact that the people from the Medical Division would probably be involved to some degree with any research that was under consideration, and decided that in spite of this possible problem the proposed composition of the committee would be satisfactory.

b. Officers of the Committee

The committee would need a chairman, who would probably be from the Medical Division, and a secretary who would be one of the consultants. Dr. Lange has agreed to serve as secretary for at least an initial period.

Decisions of the Committee

It was our concensus that the decisions of the committee would probably need to be unanimous to allow a research proposal to go forward, or at least to have the approval of both of the outside consultants. In the event that one consultant objects to a research proposal, if there is otherwise considerable support for it, other consultation would be sought. It is our impression that in most instances the committee would be able to reach an essentially unanimous opinion on each research proposal.

Relation of the Committee on Human Studies to the Existing Radioisotope Committee at ORAU Medical Division

It was our opinion that the new committee would not replace the existing radioisotope committee. Proposed studies involving radioisotopes would need to be approved first by the ORAU Isotopes Committee and then by the Committee on Human Studies. Minor changes in research involving radioisotopes could be approved by the Isotopes Committee without further ratification by the Committee on Human Studies. Copies of the minutes of the Isotopes Committee will be sent to Dr. Lange and Dr. Heyssel.

Function of the Committee on Human Studies

The Committee on Human Studies would have meetings called by the chairman at whatever frequency seemed necessary - perhaps two or three times per year. Certain problems not requiring a full meeting of the committee could be handled by telephone communications, preferably by a three-way hook-up with Dr. Lange and Dr. Heyssel. New research proposals would be written up by the senior investigator. A form for this was developed, based upon the one used at the University of Tennessee in Knoxville with suitable modifications. After the form is filled out, the proposal will be evaluated by the administrative office of ORAU Medical Division.

If approved by the chairman of the Medical Division, or considered worthy of serious consideration by the Committee on Human Studies, copies will be sent to Dr. Lange, Dr. Heyssel, and other members of the committee previous to the meeting of the committee. At the time of the meeting, further questions may be asked of the investigator and then the committee will either approve or disapprove the research proposal.

What is to be Considered by the Committee?

The committee is to review all research at the ORAU Medical Division involving human patients in which there is believed to be a significant risk to the patients or a significant possibility that criticism might be leveled at the scientists for their manner of doing studies in human beings. The decision about whether or not a specific investigative procedure involves any risk and therefore requires action by the committee would rest with the Medical Division. The Medical Division should bring to the committee's attention by name and brief description those experiments in human beings believed to have negligible risk, i.e., a systematic survey of hemoglobin and hematocrit values in thyroid patients. Considerable discussion was held about the suitability of undertaking a rather unconventional form of treatment in a single seriously ill patient, partly with the objective of immediate benefit to the patient and partly as a preliminary research effort that might be the basis for a future controlled investigation. Here the group felt that considerable leeway rests with the physician who is responsible for the patient's care. Ordinarily the Committee on Human Studies would not be involved with decisions concerning a single patient but rather with policy matters or research on groups of patients. However, if circumstances were such that the staff of the

Medical Division wanted some consultation on the suitability of a study in an individual patient it might be quite reasonable to seek telephone discussion on this.

Scope of the Committee's Work:

It was decided that the committee should concern itself with all studies done in human beings, whether these subjects are patients in the research hospital or normal volunteers of some type.

Approval of the Previously Prepared ORAU Medical Division Document on Human Volunteers and the Function of the ORAU Isotopes Committee:

Dr. Lange and Dr. Heyssel are in agreement with the document as presented. It was pointed out by Dr. Heyssel that there are certainly some risks in using employees, and that careful protection should be given to employees used as research subjects. Students are quite unsuitable for most research procedures unless the risk is nil since they are not really free to refuse to participate. Dr. Heyssel has serious reservations about using prisoners in research because here too it is very difficult to establish a situation which is free of any suggestion of coercion.

Future Meetings:

It was decided that we would try to have another meeting, perhaps in May or June, and begin to review research proposals. We decided that we should eventually review all of the significant human research at the Medical Division, including those projects that are already under way, with highest priority to review of any studies that might be of questionable suitability or subject to criticism.

Gould Andrews
Acting Secretary

OAK RIDGE ASSOCIATED UNIVERSITIES

Oak Ridge, Tennessee

Authorization for the Administration of Radioactive Substance

I hereby authorize the staff of the ORINS Medical Division to

administer to ______________________________ the following radio-

active substance ____________________ ______________________________
Nuclide Chemical

____________________ ______________________________
Dose Route of administration

The purpose of this procedure has been explained to me as being:

____

____

____

Its relevance to my condition, the risks and any possible alternatives have been explained to me.

____
Name of patient

____
Date

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

I authorize the performance upon myself
(myself or name of patient)
of the following treatment: Total-body irradiation for treatment of my lymphoma
(State nature of treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may be unpredictable.

DATE: 6 April '70 x
(Patient or person authorized to consent for patient)

WITNESS: E A Sye

I have talked with ______ ______ about
Name
the proposed course of treatment to be given himself
Name
including the following:* Total Body Irradiation 100R
c̄ LET 131

C L Edwards MD 6 April '70
Physician / Date

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee

Consent to Experimental Treatment

I authorize the performance upon ______________________
(myself or name of patient)
of the following treatment: Total body irradiation in the medium dose rate facility for control of my chronic granulocytic leukemia
(State nature of treatment)

The nature and purpose of the treatment, possible alternative methods of treatment, the risks involved, and the possibilities of complications have been explained to me. I understand that this treatment is not the usual treatment for my disorder and is therefore experimental and remains unproven by medical experience so that the consequences may be unpredictable.

DATE: 15 Nov 71 ______________________
(Patient or person authorized to consent for patient)

WITNESS: ______________________

I have talked with ______________________ about
Name
the proposed course of treatment to be given METBI 150 R. fractionated (30R/da x5
Name
including the following:* ______________________

Helen Vodopick Gowitz
Physician

15 Nov 71
Date

*Physician should indicate experimental drugs, radioisotopes, radiation therapy, and/or possible placebo or sham therapy.

Mr. GORE. Thank you very much. Finally we would like to hear from Ann Sipe, the former lab technican and you are a licensed pratical nurse if I am not mistaken.

Ms. SIPE. Yes.

Mr. GORE. Welcome. We look forward to hearing from you.

Ms. SIPE. Mr. Chairman and members of the committee, my name is Ann Sipe. I am clinical nurse with the ORAU outpatient nuclear medicine program and technician at the Radiation Emergency Assistance Center/Training Center.

From 1967 until 1974, I was lab technican for the low exposure total body irradiator (LETBI) at ORAU. My job was to familiarize the patients scheduled for LETBI with the facility and to collect data on magnetic tape from patients who were being monitored during treatment in LETBI.

As part of the familiarization procedure, I would take the patient on a tour of LETBI, show them the sources, explain how the intercom, closed-circuit television, and "umbilical" monitoring system worked.

In discussing the umbilical cord, I always discussed how this was similar to those worn by astronauts and that monitoring data collected during their exposure would be analyzed by ORAU for NASA.

Every LETBI patient from whom monitoring data was collected was informed by me before treatment of the possible use of their data for NASA.

Mr. Chairman, that concludes my statement.

[The prepared statement of Ms. Sipe follows:]

STATEMENT BY ANN SIPE, CLINICAL NURSE, OUTPATIENT NUCLEAR MEDICINE TECHNICIAN, RADIATION EMERGENCY ASSISTANCE CENTER/TRAINING SITE, OAK RIDGE ASSOCIATED UNIVERSITIES

Mr. Chairman and members of the Committee, my name is Ann Sipe. I am clinical nurse with the ORAU Outpatient Nuclear Medicine program and technician at the Radiation Emergency Assistance Center/Training Center.

From 1967 unitl 1974, I was lab technician for the Low Exposure Total Body Irradiator (LETBI) at ORAU. My job was to familiarize the patients scheduled for LETBI with the facility and to collect data on magnetic tape from patients who were being monitored during treatment in LETBI.

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Every LETBI patient from whom monitoring data was collected was informed by me before treatment of the possible use of their data for NASA.

Mr. Chairman, that concludes my statement.

Mr. GORE. Thank you very much.

There are two focuses to this inquiry as I stated earlier. One has to do with the dual goals pursued at the Medical Division and the interaction between those two goals. The second focus is narrower, a single case which forms the focus of the charges leveled against the Medical Division.

I would like to go first to the single case of Dwayne Sexton and then extend the focus to the goals of the Medical Division.

Dr. Vodopick, you were the physican technically assigned as responsible for Dwayne Sexton at Oak Ridge, is that correct?

Dr. VODOPICK. Yes, sir.

Mr. GORE. Now, the decision to irradiate Dwayne Sexton did not come until after a 3½ year period during which other forms of treatment were tried. That is correct, is it not?

Dr. VODOPICK. That is correct.

Mr. GORE. Now, the first subject issue which arises is the selection of the immunotherapy procedure, the first procedure tried. You referred to it in your statement. Was that decision yours or was it a decision by the clinical committee?

Dr. VODOPICK. That was a decision by the clinical committee.

Mr. GORE. Dr. Lushbaugh, did you take part in that meeting of the clinical committee?

Dr. LUSHBAUGH. No. I think when you refer to the clinical committee what you are really referring to is what we would call the clinical staff and where I was considered a member of the clinical staff I was not considered an essential member of the clinical staff because I was in involved in radiation accident management. I was in pathology from the point of view of what happens after radiation.

I did special studies in radiation cell sizing and nuclear medicine and the like. I was in a completely different area than the total body irradiation therapy. I came to Oak Ridge from Los Alamos largely because of the availability of the nuclear medical program and my interaction with Dr. Gould Andrews was with his interest of radiation accidents.

So that I was not a frequent participant in staff—not as it came to the treatment of patients—but I certainly participated in staff meetings concerning science and medical division plans and goals and this sort of thing because my small group was part of the staff in other words. But the staff as a committee did not really have a therapy committee. It had a meeting on all Wednesday mornings, starting very early. One religiously went to that if he was concerned with patients. Since I was not concerned with patients I was not very religious in my attendance. When one queried the clinical pathologist who was in charge of the pathology of patients he said my attendance—we asked him this the other day—was in his opinion less than 10 percent.

Mr. GORE. So there was not a formal committee with a name and a formalized identification. There was a staff meeting of the medical staff where the decisions were actually made on how patients were to be treated, is that correct?

Dr. VODOPICK. That is correct.

Mr. GORE. You attended some of those but most of them you did not attend?

Dr. LUSHBAUGH. Right.

Mr. GORE. At the staff meeting where the decision was made to try this immunology procedure on Dwayne Sexton, who suggested this procedure?

Dr. VODOPICK. This protocol was initially devised by several immunologists in conjunction with the Chairman of the ORAU Medical Division, Dr. Andrews and Dr. Lowell Edwards. The immunologists involved were Dr. Charles Congdon, who is at the UT Medical Center in Knoxville; Dr. Naz Gengozian, who is still at ORAU, plus the other two gentlemen I mentioned, Dr. Andrews and Dr. Edwards.

Mr. GORE. Now you referred to the risks involved in the immunotherapy procedure. Without objection I would like to put into the record at this point the medical program review committee's assessment of that procedure. This was in 1966 I believe. Are you familiar with that report?

[The information follows:]

The Committee noted with interest that residents are sent on a regular basis to the Division for special training from the Massachusetts General Hospital, but did not learn of any rotation of residents to the Division from hospitals in the ORAU group. What does the ORAU envisage as the future of the Medical Division in relation to its individual universities? Would the work of the Medical Division be advantaged by close affiliation with a single university?

D. Isolation

It is the considered opinion of the Committee that the staff of the Medical Division is disadvantaged by its relative intellectual and physical isolation. The physical isolation of the clinical and laboratory facility is self-evident and is believed to be unfortunate. The relative intellectual isolation becomes apparent upon discussions with the staff, and upon review of the "Research Report" and the Division's bibliography. The Committee believes that this intellectual isolation is due to some extent to the physical isolation of the facility, but is totally unable to explain the less than optimum intellectual interchange with the ORNL Biology Division. It is recognized that some of the Division staff are collaborating with members of ORNL, and that notices of seminar and lecture activities at ORNL are provided to the Division staff, but the Committee gathered the impression that vigorous intellectual interchange on a broad basis could be greatly expanded with much benefit to the Medical Division. We also gathered the impression that stimulating intellectual interchange with the parent universities of ORAU is not optimum.

The 1964 Review Committee also commented in similar vein concerning the isolation and made suggestions for alleviating the situation. The present group feels that far too little has been achieved in this respect.

The Committee suggests that the ORAU consider the problem of isolation and the possible virtues of continuing the Medical Division at its present site, or of relocating it in Oak Ridge, or in an area where it would become a part of a large and vigorous clinical and educational environment. Experience has proven that the daily intellectual stimulus provided by a community of scholars of many disciplines is invaluable, and that clinical investigation is best accomplished in a medical environment actively concerned with the care of the sick with many and diverse types of disease. Comments were made by the Director and members of the staff concerning relocating the physical plant to a site adjacent to the ORAU administrative buildings. If relocation is to be accomplished, the ORAU might wish to consider radical relocation to a site which would place the Medical Division in close relationship to a major hospital, university, or larger research institute.

Physical Facilities

The Committee questions the advisability of continuing or increasing the physical separation of various laboratories of the Medical Division. The existing location of Dr. Snyder's laboratories in the Bethel Valley facility is believed to be less than advantageous and diminishes mutual intellectual interchange between Dr. Snyder and the remainder of the staff. The proposal to construct a new facility to house Dr. Gengozian's work at a considerable distance from the main facilities of the Medical Division seems unfortunate.

The Committee believes that it would be desirable to consider centralizing all laboratories and animal facilities of the Division in one physical location, and that all factors relating to the site for this location should be carefully evaluated.

Additionally, the Committee felt that a review of already available space and its present and projected usage should be made before additional space is constructed. The Committee is of the opinion that the future mission and program of the Medical Division should be assessed before planning construction of new space.

Experience has indicated that maintenance of small clinical units, such as the Medical Division's 25-bed research hospital, independent of a general hospital is not conducive of the best clinical investigation, or of the best patient care. Additionally, the Committee expressed concern relative to the major expense involved in maintaining the Division's 25-bed unit separate from a general hospital. It is suggested that careful consideration be given to the probable significant increase in costs which will occur if the hospital is moved to a site adjacent to the ORAU administration buildings, since this would necessitate independent provision by ORAU of food and other costly services which are now purchased from the Oak Ridge Hospital.

The Committee does not clearly understand the problems attributed to A.E.C. ownership of the present Medical Division facility, or why this is disadvantageous to the program. If such ownership constitutes a major problem, it might be approached by transfer of the property to ORAU.

The equipment of the Division appeared to be very adequate in most respects. The whole body counter, and the new radiation therapy facility are unique and very elegant. The provision of a computer by ORAU from its own funds was greatly appreciated by the staff.

II. COMMENTS ON SPECIFIC RESEARCH PROGRAMS

Total Body Irradiation Program. Radiosensitivity of Man

The work in total body radiation, because of its potential contribution to knowledge of the effects of radiation on human beings, is of great practical and theoretical value and should be continued. The physical facilities of the Medical Division are such that a great variety of exposure configurations and dose rates can be accomplished.

It would be desirable to compare the results of treatment by these modalities of a variety of neoplastic diseases to the results of treatment with chemotherapy. It would be very useful to see what the effect of this type of therapy is compared to chemotherapy for a variety of other solid tumors such as carcinoma of the breast, carcinoma of the gastroenteric tract, the urogenital tract, etc., as well as for lymphomas. The addition of sham episodes would be desirable. The addition of sterile barriers for patient care is recommended as an important modality for patient care. The planned addition of a microbiologist to consider relations of the organisms of the gastroenteric tract to the integrity of the host is important.

The work of Lushbaugh in this area should be continued with a high priority because of its importance in the national interest not alone from the man-in-space program, but also from the point of view of weapons effects and civil defense.

The work of Dr. Comas in studying hypoxia and radiation in animal neoplasms is interesting. Additional background information from simpler systems would be very valuable in planning his research. Comas has recognized certain difficulties with problems of collateral circulation when using hypoxia as a technique. He could undoubtedly use another technician or diener, which seems to be his only modest request.

Cytogenetic Studies

Dr. K. O. Goh has recently been added to the staff at ORAU to provide cytogenetic support for the program. His present interests include study of the kinetic biology of the "Philadelphia" chromosome which is thought to be pathognomonic for chronic myelogenous leukemia. However, 3 of 8 patients who had been involved in a radiation accident at the Y-12 laboratory now exhibit abnormal chromosomes similar to the Philadelphia chromosome without evidence of chronic myelogenous leukemia, and Dr. Goh is seeking to elucidate the mechanism of formation of these aberrant bodies.

Using material obtained from leukemic patients, he finds differences in the generation times of Ph^1 bearing cells and is attempting to formulate a model for explanation of these observations.

Leukemia Therapy

Recently, Dr. C. L. Edwards and associates have attempted to treat a human patient with lymphocytes derived from a donor previously immunized with the leukemic patient's own bone marrow cells.

It is suggested that this immunotherapeutic approach to leukemia in humans is premature. There are many theoretical reasons why this kind of treatment should not work; and the observations of Delarme and Alexander should not be accepted uncritically.

The Oak Ridge work is based on rather sparse observations by others on animal model systems not including leukemia. Apparently the rationale of such treatment is that cell-mediated immune reactions are more important in this disease than circulating cell-free antibodies. While this could well be the case, it remains to be proven even in animal leukemia systems and certainly the burden of proof would be upon anyone proposing such therapy for humans.

Work at the National Cancer Institute has shown that vaccination with Rauscher murine leukemia virus is effective against subsequent challenge with live virus and also that neutralizing antibody of the "humoral" type is effective in reducing the viremia associated with the disease. On the other hand, experiments designed to show the effectiveness of "delayed hypersensitivity" type of immune protection have yielded negative evidence.

Although animal work involving cannulation of the thoracic duct is not easy and at present there are no leukemia-virus model systems in dogs or larger animals, there are some available tumor model systems which the Oak Ridge group should use to gain knowledge and base-line observations before establishing a program using human patients.

Deinhardt has recently reported on a Schmidt-Ruppin strain of Rous Sarcoma Virus inducing rhabdomyosarcomas in 6/6 marmosets inoculated with subsequent metastasis and death in 60-90 days. Such a system could provide the information required to establish the immune lymphocyte therapy and since Dr. Gengozian already has a sizable marmoset colony and experience in management of the animals, it should not be difficult to implement.

It was also noted that total body irradiation of leukemic patients for therapeutic purposes is still being practiced at the Medical Division. However, it is surprising that specifically directed antibiotic support therapy, platelet supportive therapy for hemorrhagic diathesis, and reverse isolation techniques are minimal or non-existent in the clinical treatment of leukemic patients.

Abundant data accumulated during the past 10 years on total body irradiation of leukemics and the ensuing complications resulting therefrom have been uniformly discouraging. Early thinking that the right dosages of irradiation would allow permanent grafts of homologous marrow has not worked in practice and given no further advances in the transplantation field; continuation of this type of experimentation could be criticized on ethical and possibly on other grounds.

COMMENTS ON THE REPORT OF THE COMMITTEE OF CONSULTANTS

by the

STAFF OF THE MEDICAL DIVISION

1. Intellectual Isolation - Relationship to ORNL and Universities (page 2)

A review of our bibliography will show a considerable number of publications indicating extensive collaboration with staff members of the Biology Division, Health Physics Division, and Thermonuclear Division of ORNL.

Dr. Kretchmar is collaborating extensively with Dr. Congdon and others at the Mammalian Recovery Group at the Biology Division. Kretchmar spends a considerable amount of his time there and on some occasions he and Congdon work here on the analog computer. The Biology Division has furnished the animal experimental material and Kretchmar has furnished the biochemical techniques on several of their projects. At one time the relationship between Kretchmar and Householder was more active that it is now. More recently Kretchmar has tended to collaborate more on the biological than the mathematical aspects of his research. He has had a fruitful and active exchange with Dr. Bernard Patten of the Ecology Branch of the Health Physics Division who has used mathematical approaches to populations that Kretchmar believes applicable to cell populations. Kretchmar has been able to offer analog computer service for Patten's work. Kretch has been active in promoting research at Knoxville College and in helping Dr. W. H. McArthur there get a small research grant. While this activity might not be considered highly stimulating scientifically, since Knoxville College is a small and underprivileged institution, we think the relationship is somewhat indicative of Kretchmar's attitude toward collaboration.

Kretchmar has significant scientific exchanges with Dr. C. W. Sheppar of Memphis and Dr. Jack Schooley of Donner Laboratory. He has been discussing problems of erythropoiesis with Dr. Eugene Goldwasser and associates at Chicago and recently made a trip there at Dr. Goldwasser's invitation to extend these discussions. Both Kretchmar and Snyder hold professorships in the Biochemistry Department of the University of Tennessee at Memphis and give a series of advanced seminars there each year. One of the members of the department has visited Oak Ridge to work on the analog computer.

With two or three justifiable exceptions, every senior staff member has meaningful communication and/or collaboration with scientists outside the Medical Division. The exceptions involve the specific research interests, personalities, and style of working of the scientists.

It is not practical to list in detail all of these relationships for each staff member. Drs. Lushbaugh and Snyder have particularly wide ranging communication and collaboration in their areas of interest. Lushbaugh has an active collaborative program on platelets with T. T. Odell of the ORNL Biology Division. Comas has recently spent nearly a year at Stanford and Snyder spent several months at the University of

North Carolina last year. Bergner works closely with Williams of Duke on several projects in mathematical biology.

We recognize the need for meaningful collaboration, and we encourage it. In our administration of the Medical Division we assume that there is room for a wide spectrum of degrees of participation in collaborative work, depending on the individual investigator's personel needs and inclinations. The opportunities are here, and strong support is given for such exchanges.

No effort will be made to list the data on travel, seminars, or the constant flow of scientific visitors (sometimes distracting). We believe that such a listing would present a picture of considerable intellectual stimulation and absence of isolation.

On the other hand it is true that we have not been able to develop the degree of participation by faculty and students of our own medical schools which we would like to have. We had a few residents from Louisville several years ago but none recently. The great majority of member schools have never had a resident with us. Few research participants come from medical schools. Two years ago we had a program review for deans of ORAU medical schools which was very enthusiastically received, but it has resulted in essentially no increase in participation. Another approach to this problem is now under consideration.

2. Trainees
(page 2)

The Medical Division has consistently worked to increase the number and quality of trainees. In nonclinical areas there has been considerable success and within the last two years graduate students have come in biochemistry and immunology, and additional students are doing course work preparatory to coming here for thesis work. These students are from both the Memphis and Knoxville campuses of the University of Tennessee and from the University of North Carolina. In the more clinical areas we, like many other medical institutions, have not been able to locate as many research trainees interested in working for one year or longer as we have wished. We have sent announcements of our openings at least once per year to all departments of internal medicine of all medical schools in the United States and to leading teaching hospitals. We have been able to fill all salaried training openings but would like to have a larger number on fellowships. The two post-resident research training positions for the coming year are filled by a man from St. Louis University and one from Johns Hopkins.

One handicap has been that we have had very limited funds in own budget for trainees. We have gotten some help from such organizations as the Picker Foundation, Abbott Laboratories, and the Damon Runyon Fund. However, it is difficult to recruit for trainees with uncertain financial support. This is one area in which we would agree that a close tie with our medical schools could be of value.

Incidentally, we believe that we would have no difficulty getting short-term residents like those we get from the Massachusetts General Hospital. We agree with the committee that the real need is for longer-term trainees. It is virtually impossible to get fellowship support for persons in clinical residency training, and we are not able to increase the use of our operating funds for this purpose.

During calendar year 1965 we had the following trainees:

One year or longer	- clinical	7
	- graduate students	2
	- postdoctoral	1
Shorter periods (usually 3 months)		
	- radiology residents	5
	- research participants	7
	- Abbott fellows (senior medical students)	5
	- undergraduate students	7

In addition, our staff actively participated in the Medical Qualification Courses given by the Special Training Division of ORAU with lectures and clinical demonstrations (four 3-week courses given each year).

3. The Question of Isolation of the Clinical Unit
(page 3)

We recognize some negative aspects to this setting for a clinical unit, such as lack of a large pool of patients that could be used briefly and immediately transferred back to patient care wards, and lack of easy contact with certain specialized clinical facilities.

On the positive side are the following:

1. We have been able to get all needed clinical material for research projects, drawing on a large area of surrounding states.

2. We have been able to establish really close collaboration between clinical and nonclinical scientists on clinical problems. In addition to the intensive research programs here, we have furnished patient specimens of a variety of types to many investigators at ORNL, in Knoxville, and at Memphis.

3. The rapid growth of nuclear power and usage of radioactive materials in the nation results in a continuing increase of potential sources of radiation accidents, even though health physics measures are superb. Oak Ridge is a logical site

for a team of clinical experts familiar with the uses of radioactive material and the management of radiation accidents.

4. While it is true that this clinical unit is somewhat isolated, it is equally valid to emphasize that these very features make it desirable to strengthen the facility as an important viable nucleus for growth and development in an area where there is medical and scientific need for such a resource.

The questions raised by the committee are so stated as to imply negative answers. It is impractical to move the Medical Division to a city where there is a large medical center. A more creative approach would be to support efforts to make the program grow and flourish here.

Total Body Irradiation
(page 5)

The suggestion is made that we should treat carcinoma of the breat, gastroenteric tract, and urogenital tract by total body irradiation. These groups of patients have been carefully considered for such therapy, and we are very hesitant to treat them because we believe there is so little chance of benefit to make it questionable ethically to treat them. Lesions that require-moderate or high doses of local therapy for benefit, or that are actually resistant (gastroenteric tract) are not helped enough by total body radiation to justify the bone marrow depression that is induced. Of course, in one way these patients would make good subjects for research because their hematologic responses are more nearly like those of normals than are the responses of patients with hematologic disorders.

3. Leukemia Therapy
(page 7)

We would like to emphasize that of all the work presented at the program review, the studies on immunotherapy of human leukemia most clearly represent collaboration with the Biology Division of ORNL. Dr. C. C. Congdon has been a prime mover in encouraging us to undertake this effort. We agree that such a technique might be even more appropriate for solid tumors than for leukemia, and we had already tried the use of thoracic duct lymphocytes from a non-sensitized donor in a patient with melanoma. We plan further efforts in solid tumors. The work with leukemia has been discussed with many persons competent in the field and has been considered an important and justified approach. It has been discussed by Dr. Edwards and Dr. Congdon at the conference held December 2-3, 1965, at the U.S. Naval Radiologic Defense Laboratory in San Francisco and has been considered by the Southeastern Task Force on Leukemia of the National Cancer Institute. Dr. Andrews discussed the work in detail with Dr. Georges Mathé and his staff in Paris. The journal, Experimental Hematology, put out by the Biology Division of ORNL contains information on this; see Vol. 9, 1956 (cover, comments on cover, p. v, and abstract, p. 23). We have given prolonged consideration to the ethical aspects of this work, mainly in relation to the risk taken by the donor. The surgical risk is very small. We know of course that the radiation of the sensitizing cells will not kill viruses. There is no reported evidence that a preparation of killed leukemic cells can induce any disease in an adult mammal.

We recognize that with any new therapeutic attempt in human beings serious questions can be asked, and we appreciate the committee's very serious concern. We do insist, however, that this program has not been developed in isolation, and in fact it represents a clear example of collaboration.

Among audiences hearing this work, made up of persons more knowledgeable in experimental therapy of acute leukemia than any member of our review committee, no such negative attitude as that represented in the committee report has been expressed.

On page 7, next to last paragraph, are comments relating to total body radiation of leukemia. These comments fail to distinguish the two types of therapy described to the committee: A - low dose therapy of chronic blood disorders; B - high dose therapy of acute leukemia.

Low dose total body radiation is widely accepted as a suppressive measure in chronic leukemia and lymphoma. It gives excellent results in chronic granuloytic leukemia and appears quite effective in lymphosarcoma. The treatment of chronic lymphocytic leukemia is a controversial problem, as the staff of the Medical Division is well aware, but suffice it to say that, if any suppressive therapy, such as chlorambucil of P^{32} is to be used, total body radiation will give comparable results.

The continued study of the low dose treatment of these chronic blood diseases seems to be justified.

The use of larger doses in acute leukemia was started in an effort to achieve homologous marrow grafts. We have, for the moment, abandoned attempts at marrow graft therapy, awaiting improvements that will give a better chance of success, but we have not abandoned the possibility that this may eventually become a feasible therapy. An interesting observation we have made is that large doses of total body radiation will give brief remissions in some patients with acute leukemia who have exhausted the benefit of combined drug therapy, and in a few cases we are using such therapy as a rather desperate last measure, with valuable observations on radiation effects.

The remarks about isolation techniques, antibiotic therapy, and platelet therapy call for further comment. It is true that we have very limited isolation facilities, although our interest in this area is documented by our budget requests for several years. We are currently in active contact with the NIH and University of Minnesota, with the help of comments made by Dr. Stevenson at the program review, about laminar flow arrangements. Earlier we had visited the clinical center of NIH and Walter Reed Hospital to consult on plastic tent isolators.

Antibiotic therapy has not been given without bacteriologic studies on our patients; we have extensive data on infecting agents, which we plan to publish, gained with the help of the bacteriology laboratory of the Oak Ridge Hospital. However, we have felt the need for a highly trained microbiologist who could go into this project from a research approach and hence the AFEB project and employment of Dr. Balish.

We separate platelets by the techniques used elsewhere and use such therapy frequently. Sometimes we have donors with polycythemia or other myeloproliferative disorders who can give very rich platelet material. We have collaborated on platelet problems with Dr. T. T. Odell at the Biology Division. Our standard technique for platelet counts was improved with the help of Eugene Cronkite at the time of the Y-12 accident in 1958. Dr. Lushbaugh and Dr. Odell are interested in platelet counting by the Coulter principle. We are making limited use of white cell therapy and have been closely in touch with Dr. Emil Freireich on this problem.

6. Whole Body Counting
(page 9)

We believe that the design and testing of the whole body counting instrumentation, although not an end in itself, has clearly proved to be worth-while scientific contribution in its own right. A great deal of valuable information was collected in the study program searching for low activity shielding materials and characterizing the features needed for low background whole body counting. The unit has been carefully calibrated and has found use already in studying the turnover of radioactive tracer compounds in thyroid disease and hemopoietic disorders. It has also been a service resource to the Tennessee Valley Authority in monitoring employees working on an experimental reactor project.

We have not been oblivious to the desirability of using the counters for metabolic studies. We concur with the committee's hope and fully intend to exploit this elegant resource. The addition of a clinician specializing in metabolic problems has had a rather high priority in our thinking, but limited budget has impeded us in this area. We do not share the view that the clinical material to occupy this counter will be unobtainable.

7. Radioisotopes in Diagnosis
(page 10)

The Medical Division has only recently given intensive study to the preparation of radiopharmaceuticals. The staff now working on this were previously mainly engaged in programs related to chemical dosimetry and rare earth metabolism. Now that Ga^{68} is clearly shown of value for bone studies, efforts are concentrated on developing a colloidal preparation of this isotope for studies of liver, spleen, and marrow. Dr. Hayes' ideas of using iron hydroxy colloids as a scavenger vehicle appear to have merit and are being taken up by Dr. Paul Harper's group at Chicago. Studies on Indium 113 are next in line and a generator is already available.

Dr. VODOPICK. I did not see it until last week.

Mr. GORE. So you just saw this for the first time last week?

Dr. VODOPICK. Yes, sir.

Mr. GORE. The medical program review committee says—I take it this refers specifically to Dwayne Sexton—

> Recently Dr. C. L. Edwards and associates have attempted to treat a human patient with lymphocytes derived from a donor previously immunized with the leukemic patient's own bone marrow cells.

It is suggested that this immunotherapeutic approach to leukemia in humans is premature. There are many theoretical reasons why this kind of treatment should not work; and the observations of Delorme and Alexander should not be accepted uncritically. It goes on to say the work was based on rather sparse observations by others on animal model systems not including leukemia.

What was your reaction when you found out about this last week?

Dr. VODOPICK. I was surprised but I did not think it was unexpected. I think we don't enjoy the harmony and accord that Congress has. I know I have been reading in the paper——

Mr. GORE. I don't know——

Dr. VODOPICK. I have been reading in the paper when somebody says sell AWACS to the Saudis everybody agrees and when somebody says cut tobacco subsidies everybody disagrees. I assure you it is not the same way in medicine. If you ask 1 question to 10 different physicians you are probably going to get 10 different answers ranging from yes, maybe, I don't know, no opinion, to no. And I think we had some very substantial, very outstanding immunologists who concurred with this type of treatment and therefore it does not surprise me that you find somebody on the other side of the fence who is disagreeing with that type of therapy.

I think in addition at the end of that critique Dr. Andrews did give a rebuttal which also stated his position that he felt that there was sound data and that something new should be tried to try to prolong the life of these patients.

Mr. GORE. Without objection, we will put that in the record also, but I am surprised that the clinical staff was not made aware of the medical program review committee's judgment on this matter at the time. Why would that be?

Dr. VODOPICK. I guess Dr. Andrews felt strongly enough that the program was sound and viable that he did not need to burden the medical staff with this information.

Mr. GORE. Did you in fact believe that this had never been done in human beings before?

Dr. VODOPICK. I had never perused the literature prior to that time. I came in July 1965 so this is when Dwayne Sexton was first admitted, in July 1965.

I had been at two university hospitals in training for the previous 4 years before coming to ORAU; I had been intimately involved with the care of leukemic patients and I saw that they died. The ones we took care of at the university hospitals all died. They were involved in drug protocols in which they were randomized to different studies. In other words, these were double-blind studies. Even the physicians who were giving the drugs did not know what they were giving. One patient was assigned to one group. Another patient was assigned to another group and the drugs were dispensed by a pharmacist. The code was not broken until the study was concluded. So that truly is a double-blind study.

Therefore I knew that the risks were quite great to anybody who had acute leukemia at that time. There was a certain element from the testimony—I don't know if this is an appropriate time to add this—one page that was not read at the time. Do you want me to read this?

Mr. **Gore**. Fine.

Dr. **Vodopick**. The beginning of the paragraph stated.—

> In the present year 1981, the survival statistics of acute lymphocytic leukemia have improved significantly but still only 50 percent of the children treated are alive at 5 years and only one of two of these children are expected to live beyond 10 years.

This is the part that was left out—"these are better survival statistics but still not good enough."

Further drugs are needed and new and different approaches still need to be tried. Probably in another 20 years, people will look back on this decade and question how such crude methods could have been used.

Another caveat should be mentioned. The children today are still receiving 2,400 rads whole brain irradiation. No one can say with certainty that this therapy will not leave these children with some mental or physical impairment in the future. In fact, children have died with a condition called leukoencephalopathy, a condition directly related to brain irradiation. What is good and acceptable today may be obsolete and abandoned in a few years.

Unfortunately the other types of chronic leukemias in adults have not fared as well as childhood lymphocytic leukemia. Patients with advanced chronic lymphocytic leukemia had a median survival time of 3 years in 1965–69 which remains the same today. The median survival time for patients with chronic myelogenous leukemia was 3.5 years in 1965–69 and is the same today.

Radiation did not prolong nor shorten survival time; drugs have not improved survival time in these diseases; something new and innovative should be tried.

Therefore I think that even though the survival statistics are much better for these acute leukemia patients there still is potential risk. On Monday at a review course for cancer I saw some very lovely but very frightening slides of children who had died with leukoencephalapathy. They had undergone brain degeneration. They develop cysts of the brain and some have a very, very short course after they develop this condition.

So, it is hard to believe that giving 2,400 rads to the brain will not carry a definite risk; however, this is done a certain purpose—those children were originally known to relapse because their leukemic cells sequestered in certain areas of the body where the drugs could not reach. Therefore something had to be done to try to get to these leukemic cells so they could not reinvade the body and reestablish a leukemic situation.

Therefore St. Jude's Hospital in Memphis, Tenn. was the pioneer of this type of therapy. And in answer partly to Mrs. Sexton's question about this long survival that St. Jude was having—I do know they started this program of whole brain irradiation in 1962 but they too were very cautious.

They did not start with 2,400 rads. They started with 500 rads in 1962 hoping that this was sufficient to eradicate those leukemic cells.

When they found this did not make a dent in their survival statistics they upped the dose to 1,000 rads and then in a few more years when they found that this dose did not do the job they used 2,400 rads. So you have to start at a reasonable dose and then gradually increase the dose as you see the effect is not what you want. Therefore, they are still doing this treatment and this is an accepted procedure throughout the United States now, in combination with drug therapy.

Mr. GORE. So as the physician with principal responsibility for Dwayne Sexton and as a member of the staff which together made the clinical decisions you chose this experimental immunotherapy procedure in hopes that the unknown chances of its success would be greater than the small chances of success with conventional treatment at that time?

Dr. VODOPICK. That is right.

Mr. GORE. After this first relapse—let me correct the record incidentally to indicate that there were four relapses?

Dr. VODOPICK. That is correct.

Mr. GORE. With this patient?

Dr. VODOPICK. He had several admissions but they were not because his leukemia had relapsed. It was because he had additional infections and he had to be readmitted to treat those infections.

Mr. GORE. So there might have been more readmissions but four specific relapses?

Dr. VODOPICK. That is right.

Mr. GORE. After the first relapse you then embarked on a conventional chemotherapy trying one——

Dr. VODOPICK. No; that is not correct. He was started on what was considered conventional chemotherapy within 9 days after he was first admitted. That is what I gave in the testimony. The reason for waiting 9 days was to obtain enough leukemic cells by means of bone marrow aspirates from him. These cells were irradiated and given to his mother before he was put on any chemotherapy.

But I can hardly call waiting a week and a half a delay in starting chemotherapy. Methotrexate and prednisone were the accepted drugs that were used at that time, two of the accepted drugs. There were other drugs also.

Mr. GORE. Then the chemotherapy was stopped when the lymphocytes were reinjected from his mother?

Dr. VODOPICK. That is correct. It is even done today. When you give chemotherapy drugs, you give them to the point where you have eradicated the leukemic cells and a large portion of normal cells in the bone marrow because the drug therapy is not selective. You do harm to normal tissue as well as to abnormal tissue.

So, there has to be a point in time when you stop those drugs or otherwise you will kill the patient. His bone marrow at that time when the drugs were stopped did evidence hypocellularity. The bone marrow had been—I don't know if you could say wiped clean—but it had been sufficiently suppressed to warrant stopping the drug. That was when the lymphocyte infusions were started.

Mr. GORE. But a course of conventional chemotherapy would have called for continuation of the chemotherapy, wouldn't it?

Dr. VODOPICK. Yes, sir. Maintenance.

Mr. GORE. But maintenance chemotherapy was discontinued, correct?

Dr. VODOPICK. It was never started at that point.

Mr. GORE. Why?

Dr. VODOPICK. Because in order to assess whether we had done anything with these lymphocyte transfusions you had to have some parameter to measure and therefore in order to evaluate the effectiveness of this we did have to withhold those drugs in order to see whether we had really done what we had hoped to accomplish.

Mr. GORE. Then this is a decision and a dilemma not unique to the Oak Ridge medical division, but it is an example, is it not, where the interests of the patient and the interests of the medical community in finding out more about experimental procedures do come into conflict, isn't that correct?

Dr. VODOPICK. That is correct.

Mr. GORE. And the interests of the patient in this regard were subordinated to the desire to accurately assess the viability of the new procedure?

Dr. VODOPICK. I don't know if they were disregarded. I think——

Mr. GORE. Subordinated I said.

Dr. VODOPICK. Subordinated. Well, I am not even sure they were subordinated. We knew what the risks were as far as his survival from acute leukemia and I think if you are trying any new experimental procedure you have to take the risks that are involved with trying this procedure.

Mr. GORE. Now, after the immunotherapy failed then you embarked upon chemotherapy?

Dr. VODOPICK. Right.

Mr. GORE. Then that continued for a period of 3 years and more, and then came the final blast crisis. At that point was the decision to suggest total body irradiation made by the staff in a joint meeting?

Dr. VODOPICK. When he returned—I believe that was in December of 1968—he had become refractory to all the conventional chemotherapy agents that were available. Over the course of the 3 years we had to keep varying the doses and varying the types of drugs because these leukemic cells are very smart. They become resistant to drugs and therefore you have to keep giving different drugs in order to keep them under control.

Eventually you run out of ammunition. There is just nothing else that you can do; so when he came back in December of 1968 we had exhausted everything that was commonly used. There were a couple drugs I believe that were being tested and even these would have been quite experimental because they were not proven to work at that time.

So, if you want to say you were substituting one experimental procedure for another that would be certainly correct. The other options were just to give him blood and keep him alive as long as possible and a third option was to give him total body irradiation which had been shown to work in a fair number of—a small number I should say—of leukemic patients as far as producing another remission.

Mr. **Gore**. That was designated as a preferred option?

Dr. **Vodopick**. By the medical staff, yes.

Mr. **Gore**. That was done in a staff meeting?

Dr. **Vodopick**. Yes, sir.

Mr. **Gore**. Dr. Lushbaugh, did you attend that staff meeting?

Dr. **Lushbaugh**. No, sir.

Mr. **Gore**. You definitely did not?

Dr. **Lushbaugh**. I did not know of the Sexton boy problem and the other day when I was talking about this with Dr. Vodopick she said in 1965 she did not know of the NASA study group. So it is a small world.

Mr. **Gore**. So you did not participate in the staff meeting that selected the total-body irradiation option as the preferred position for this final blast crisis; you obviously concurred in the decision to go to the total body irradiation?

Dr. **Vodopick**. Yes, sir.

Mr. **Gore**. Why was Dwayne Sexton irradiated?

Dr. **Vodopick**. Well, his bone marrow had shown complete relapse of his leukemia. In other words, the bone marrow had been completely replaced by these leukemic cells. In order to suppress the cells, you had to do something to eliminate them from the bone marrow. It has been known that radiation would do this. This is why he was given total body irradiation. In other words, you try to wipe the slate clean to get rid of all the cells in the bone marrow and hope that the normal bone marrow cells will come back.

Mr. **Gore**. All right. What you are saying is that you irradiated him, as a last resort to try to save his life?

Dr. **Vodopick**. That is correct.

Mr. **Gore**. And it is your testimony that the goals of collecting data for general radiobiological interests or for NASA did not enter into that decision?

Dr. **Vodopick**. Absolutely not. No one ever discussed NASA, AEC, or any other agency. They only discussed the patient. I assure you, I had three small children at the time and it would have really been against my conscience to do anything to harm another individual.

Mr. **Gore**. Immediately after he was irradiated he was taken up to the LETBI facility and this NASA equipment was put on him by a technician being paid for with NASA funds, and that gives rise to the conjecture that information was taken because of the interest in data for NASA. You are saying that that is just not the case?

Dr. **Vodopick**. No, that is not the case. Dwayne, as his mother pointed out, was very susceptible to infection. He may have had a staph infection at the time, but that was no reason to withhold irradiation. At previous times when he had staph-septicemia, we started reinduction therapy with drugs right away. Since we didn't withhold drugs, there was no reason to hold radiation therapy because he had an infection.

But his immune response was so suppressed that he really couldn't contain the infection. Unless you do something to reverse the situation in the individual, they have no ability in their own body to fight the infection. Therefore, we tried to keep him sequestered as best we could from the rest of the hospital population. Therefore, he was put into this patient room, which was called the LETBI facility. This was quite an ideal facility because it had closed circuit TV. The nurses could watch him from the nurse's station without ever having to go into his room. The monitor was put on him initially and I don't remember at whose direction, but mainly to keep close tabs on his pulse and respiration so that people wouldn't have to keep going in and out of his room. This was done as a direct monitoring procedure, as you do in a normal hospital situation. You have to measure the vital signs if you want to know what is going on with the patient. It wasn't done in anyway associated with NASA

Mr. LUSHBAUGH. May I make a comment there?

Mr. GORE. Yes. Move the microphone closer.

Mr. LUSHBAUGH. Yes, sir.

Putting the belt on a person in the LETBI facility was part of the routine of using the LETBI facility. It was like "standing orders" that always happened. If you would put up a person in the LETBI facility, I didn't have to tell Mrs. Sipe, who was the technician who was in charge of the monitoring equipment and the person who was on standby there, that she was supposed to put the belt on the person, because that was part of the routine. When a person went in there, he got the belt on, that was the rule. That is the way I see it and the way I remember it. That is the way I set it up.

Mr. GORE. It is a little confusing because the facility where he was placed was intended to be used as a low-exposure irradiation facility, but during this period of time it was not being used for that purpose; is that correct?

Mr. LUSHBAUGH. Yes. That was only because the clinical staff didn't select a patient to be treated during that time. It was not closed down or not being used for any other reason or purpose. It was just the fact that there wasn't a patient at that time who the clinical staff felt should go into the LETBI facility and be treated.

Mr. GORE. Mrs. Sipe, you were the technician at the LETBI facility?

Ms. SIPE. Yes, sir.

Mr. GORE. When Dwayne Sexton was brought up to the facility from the METBI irradiator, you went in and placed the umbilical cord around his waist; is that correct?

Ms. SIPE. I placed the belt around his waist and the electrodes on his chest.

Mr. GORE. Now, why did you do that?

Ms. SIPE. First off, to watch for respiratory, respiration problems. We also had the strip chart going out at the console so that the physicians and the nurses could come in and see that his heart rate and his pulse rate were right and that is why the strip chart was going. The magnetic tape was not going. The belt was removed in about an hour and a half. It was unfair to keep Dwayne lying very still. The belt was made for adults, it was not made for children. And the belt would keep falling off. Also I noticed, the electrodes having been on his chest an hour, hour and a half, there was a slight irritation on Dwayne's chest, and I told the doctors that I was taking it off instead of taking the chance of more irritation on his chest. So after about an hour, an hour and a half, it was removed and never put back on.

Mr. GORE. OK. Now, your check was being picked up by NASA?

Ms. SIPE. No, sir, I was paid by Oak Ridge Associated Universities. It has that heading on my check.

Mr. GORE. You felt you were an employee of Oak Ridge Associated Universities?

Ms. SIPE. Yes.

Mr. GORE. Did you know that NASA was reimbursing AEC with funds for your salary earmarked?

Ms. SIPE. No, sir. This is never stated to employees, who pays you out of the different funds. I was hired to work for Oak Ridge Associated Universities, and that is who I work for.

Mr. GORE. OK, let me move from that focus to the two goals of the facility. Excuse me.

Mr. WALKER. Could I interrupt just a moment? I want to get something clear in my mind. Do I understand correctly that the reason for moving Dwayne Sexton to the LETBI facility was to put him in medical isolation, that he was not moved there for any additional radiation treatment at all; this was the facility that you had within the hospital that allowed you to isolate him and monitor his condition and so, therefore, you moved him into that facility for that purpose and for no other purpose?

Mr. LUSHBAUGH. Correct.

Mr. WALKER. Is that correct? So there was no monitoring of him going on to collect data for NASA purposes when he was in the LETBI facility?

Mr. LUSHBAUGH. The monitoring being done on him was started on him because that was the routine of persons being put in the LETBI facility. This was the first time, however, that anybody had ever been put in the LETBI facility to use it as a sterile facility. In the other situations it had always been for radiation purposes.

Mr. WALKER. It is this kind of isolation procedure where a patient of this type—is that standard medical practice to isolate a patient who is in the same kind of condition that Dwayne Sexton was at that point?

Mr. LUSHBAUGH. We were trying to build at the time a laminar flow facility, which would allow the patient to be in the facility where the air came across in a laminar way and blows across him in such a way that it takes his own bacteria away from him.

Mr. WALKER. You didn't have that at that point, is that right?

Mr. LUSHBAUGH. We were building it at that point.

Mr. WALKER. What you had was the LETBI facility, which was the best thing you had available given your circumstances?

Mr. LUSHBAUGH. Correct.

Mr. WALKER. So you utilized that as your isolation facility at that point, with no intention of using it as a radiation facility, simply as an isolation facility?

Mr. LUSHBAUGH. Exactly right.

Mr. WALKER. Thank you, Mr. Chairman.

Mr. GORE. You addressed this question when you responded to the question as to why he was placed in LETBI. Let me ask you pointblank: When you found he had a staph infection on the morning of the radiation, why did that not lead you to delay the radiation procedure?

Dr. VODOPICK. His platelet count was already suppressed, which meant he had a potential to bleeding into any site in his body including his brain, and if you don't do anything to eradicate these leukemic cells the condition would not only be worse, it would worsen. Therefore, we felt the situation was great enough we should go ahead with the radiation rather than to wait until he died.

Mr. GORE. Who decided the size of the dose, 353 Roentgens?

Dr. VODOPICK. That I can't answer.

Mr. GORE. Dr. Comas, did you decide the size of the dose?

Dr. COMAS. No. I don't recall the particular patient or the time when we decided what dose to give. I think I can answer from what I remember about our operation. This dose, I am sure, was decided on the basis that we felt comfortable with it. We had irridiated before the Sexton boy, several children with doses of this magnitude. We knew we could get away with it. So this was considered to be a dose that if it would not work, at least it would not harm him.

Mr. GORE. OK.

Now Dr. Lushbaugh, is it true that all of the patients that were irradiated at Oak Ridge were of interest to you as part of the work that you were doing for NASA? In other words, were you interested in the physical reactions and the radiosensitivity of all the patients that went through the facility?

Mr. LUSHBAUGH. Yes, I was. I started out, as you know, looking at some 100 patients who had been irradiated in the facility before I arrived there. It was used as a group of patients for a feasibility study to see whether or not we could take these charts and records and analyze data from them and extract from them information that could be used radiobiologically.

We used the 100 patients from the ORINS hospital, plus some from the City of Hope and some other hospitals, to try to get up to speed and set up an encoding system, a data collection system and then an analyzing system to see what we could do with these data. This had not been tried before on such a large scale.

As you recall, we finally came up to where we analyzed about 2,500 patients from all over the United States from some 45 hospitals in addition to ORINS. So, yes, we were quite interested in everything that we could find out. At that level, those were retrospective studies, and you know we have discussed several time today what the difference was in prospective studies.

I thought it was said, quite correctly, that one engages in prospective studies because one knows what kind of information he needs and try to see whether you can get information from a chart that allows you to answer questions that have been posed by other radiation biologists.

You may or may not know that one of the symptoms of radiation toxicity is a symptom called fatigue. Irradiated persons get very tired. We found as we looked at the retrospective information that we could see in some cases that the patients were fatigued. And in the famous Y12 case, the five patients who were hospitalized as a result of their accidental exposure, all of these persons were completely fatigued.

But we found when they looked at their hospital charts there wasn't any record about the fact that the Y12 patients irradiated with huge doses, around 400 rads, that they were completely fatigued when they left the hospital 6 weeks after they were irradiated. The only way that came out, was, when they tried to cut the grass at Oak Ridge they were unable to run the lawnmower.

It became obvious that fatigue caused by radiation was not going to be noted by the nurses and the nursing staff as a symptom because the patients were lying in bed and no one was testing them to see whether they were fatigued or not.

So it was obvious then, in these patients who were going to be irradiated, if we were going to measure the fatiguability of the patients we had to come up with some physiological monitoring system to see whether or not persons irradiated were unable to do exercises the way other persons did, whether they were tired, whether their stamina went away or came back or what.

So we did look prospectively to see what the effect of radiation was in particularly men, though women also participated in this, to see how they worked on an exercise bicycle. And we measured their inability to exercise or to exercise, depending on these systems. This is what the prospective studies were all about, trying to supply data that wasn't usualy obtained by clinical means.

For instance, one of the symptoms of radiation toxicity is the loss of appetite, but you don't know your appetite has been lost until somebody asks you whether you want to eat. It was that kind of a situation. You have to ask the right questions sometimes to elicit the right signs and symptoms. So this is what the design of the prospective studies was, to try to refine some of these areas where our retrospective studies came up with big voids in the information.

Mr. GORE. Now let me ask you about the 1970 publication that has been discussed previously.

Dr. LUSHBAUGH. ORAU-112.

Mr. GORE. ORAU-112, published in December of 1970. Now this publication purports to describe the entire TBI program dating back to 1957, but including the NASA period from 1964 onward.

Dr. LUSHBAUGH. Not exactly. It is about the METBI patients. It is about the hematologic effects of the METBI patients. That is as I recall it.

Mr. GORE. We have already put this in the record previously, but——

Dr. LUSHBAUGH. Isn't that what the title is, though? Isn't that the hematologic response?

Mr. GORE. "Hematologic and Therapeutic Effects of Total-Body Irradiation 50 R to 100 R in Patients With Malignant Lymphoma, Chronic Lymphocytic and Granulocytic Leukemias and Polycythemia Vera."

Dr. LUSHBAUGH. Does it say in the "Introduction" whether this is LETBI or METBI?

Mr. GORE. It does not identify METBI.

Dr. LUSHBAUGH. Those are single doses at 50 R, 100 R rather rapidly delivered, in my recollection.

Mr. GORE. It says, "The present report covers the therapeutic and hematologic results of a 10-year study—1959 through 1968—of single exposures of 50 R and 100 R." That would be METBI?

Dr. LUSHBAUGH. METBI.

Mr. GORE. METBI, all right; but it specifically discusses the goal of acquiring data for NASA and it says—

> It was not our plan to evaluate the long range effectiveness of these relatively large individual doses of total body irradiation as repetitive and sole therapy. This would have required establishing a total treatment plan with this technique, which we were not prepared to do.

And then it goes on to say—

> One should not infer from this study that we expect these individual or infrequently given exposures to produce better clinical results than fractionated or total body or portal irradiation.

Dr. LUSHBAUGH. There is a key word in the first sentence——

Mr. GORE. Yes.

Dr. LUSHBAUGH. That explains, I think, what Dr. Andrews meant. It says "sole therapy." Do you see the word "sole"?

Mr. GORE. Yes, I do.

Dr. LUSHBAUGH. Now what he means is that, "we did not intend to evaluate total body irradiation as the sole therapy." He goes on in the last sentence that you read to say the reason why it couldn't be used as the sole therapy is because he wanted to reserve the rights and privileges of modifying the protocol at any minute for the benefit of the patient, and to include chemotherapy and other drugs. And you find as you go through the charts of those persons that they all received various kinds of therapy, not just total body irradiation. So one couldn't accumulate a group of total body irradiation only patients to compare with, say, methatrexate only patients, and have these persons get the same treatment repetitively over time. Just because a person was admitted on one kind of treatment schedule and got total body irradiation did not prevent him the next time he would come in to be on methatrexate or something else, and so we couldn't do what we would call a phase III study. And at that time when Dr. Andrews was writing that, he is not talking phase I, phase II, phase III, but what he is saying is that you could not do a Phase III study using the METBI facility because you are always using other types of what you would say are çompeting risks from other therapy.

Mr. GORE. For the record, you are also listed as an author of this, and Dr. Vodopick and Dr. Comas along with Dr. Andrews, Edwards, and Kniseley.

Dr. LUSHBAUGH. It was 1 year after Dr. Comas left the staff.

Mr. GORE. Yes; but it is your testimony that Dr. Andrews was the principal author and that you all did not contribute to this?

Dr. VODOPICK. I didn't contribute to it; no.

Mr. GORE. Dr. Comas?

Dr. COMAS. I am sorry, I didn't understand the question.

Mr. GORE. You are listed as one of the authors of this.

Dr. COMAS. Yes.

Mr. GORE. Is it your understanding that Dr. Andrews was the principal author of this?

Dr. COMAS. Yes.

Mr. GORE. All right.

Dr. **Lushbaugh**. I believe Dr. Andrews is paying off obligations to staff, which was a common——

Mr. **Gore**. By giving you some credit for it?

Dr. **Lushbaugh**. Right.

Mr. **Gore**. Now in the progress reports to NASA there are a number of instances where you say to NASA—

> Total body irradiation therapy of patients will be continued in the present TBI facility at the established rate. Special attention will be given to the effects of repeated doses in the same patient.

On a number of other occasions you say to NASA, in 1965, for example, "A significant series of patients will be treated in LETBI during the year." Does that mean that patients would be assigned to LETBI in order to achieve a significant number of treatments, in order to satisfy NASA's need for data?

Dr. **Lushbaugh**. I think what you are reading there is not a progress report but it is a work proposal, and those are an expression of my hopes, and my hopes were not very often achieved, because as you saw in some of the graphs that I appended to my testimony, that the major number of patients in LETBI in any one year was about 10. Our use of the LETBI facility, which gave us some opportunity to see the effects of protracted radiation, never came up to what my expectations were or what I thought I was going to be able to achieve in a year, and if you would ask me I would say I was disappointed.

Mr. **Gore**. So you told NASA that you hoped to get more patients irradiated in the facility but what you meant by that was that you hoped that in the normal course of clinical treatment——

Dr. **Lushbaugh**. Exactly.

Mr. **Gore** [continuing]. Would result in choices that would lead to a larger number of patients being irradiated?

Dr. **Lushbaugh**. Right.

Mr. **Gore**. Is that what you are saying?

Dr. **Lushbaugh**. That is what I am saying, right.

Mr. **Gore**. Now the question arises then, you know, since you were a sometimes member of the clinical staff meetings, did your hopes and desires that the treatment would lead to larger numbers of people being irradiated ever express itself in the form of influence during the clinical staff meetings to choose irradiation over and above some other treatment where a judgment call was involved?

Dr. **Lushbaugh**. I think that the right answer to that is that with the clinical staff that we had, Dr. Andrews and particularly Dr. Edwards, and Dr. Kniseley, who were firmly entrenched in their determinations to not do anything wrong to the patients and to do what they needed, that if I had voiced any such comments, why, they would have been noted and passed over.

Mr. **Gore**. Did you express any such comments?

Dr. **Lushbaugh**. Well, knowing my personality, I would be surprised if I didn't. But I don't think that Dr. Andrews would have paid a whole lot of attention.

Mr. **Gore**. On another——

Mr. **Walker**. May I follow up on that, Mr. Chairman?

Mr. **Gore**. Sure.

Mr. WALKER. On that point, you were, however, interested in specific kinds of information; isn't that true?

Dr. LUSHBAUGH. Yes.

Mr. WALKER. For instance, as NASA pointed out this morning, you were interested in data from adult subjects primarily?

Dr. LUSHBAUGH. Right.

Mr. WALKER. If you had made that kind of a suggestion in a meeting, it certainly wouldn't have been—well, I shouldn't put words in your mouth, but it doesn't sound to me as though it would have been in the case of an adolescent or a child, because that data wouldn't have been particularly useful to you in terms of your study. Is that correct?

Dr. LUSHBAUGH. Yes.

Mr. WALKER. Do you know of any instance where any information with regard to adolescents was ever transmitted by you to NASA?

Dr. LUSHBAUGH. We never transmitted any data per se to NASA. We transmitted results of analyses and descriptions of things that we tried to do, how we tried to reduce large numbers and long tapes of pulmonary impedance and used power spectral analysis, and this is what the computer was all about; trying to take patients who had similarities and try to group them together and see what the validity of our answers was; and using that sort of thing, those answers were transmitted to NASA but that we never, for instance, made an abstract of a chart and took persons' names off of it and gave NASA the data, because NASA wasn't doing these analyses on our data. We were supplying them with what I would have called radiobiological answers.

Mr. WALKER. In the information that you provided to NASA, to your analyses——

Dr. LUSHBAUGH. Right.

Mr. WALKER [continuing]. Was there ever any information used there that had been drawn from adolescent patients?

Dr. LUSHBAUGH. Not that I know of.

Mr. WALKER. Again, is that because that was not of particular use to you in terms of what the NASA contract was hoping to achieve?

Dr. LUSHBAUGH. Well, it could have been of use to me, except for the fact that the children who were involved in these radiation therapy experiments were all at these relatively high doses, around 300 R, and at that level they always got various kinds of antihistaminic sedatives and other kinds of drugs which would help them withstand the toxicity of such levels of radiation. And I wasn't studying the efficacies of drug therapy for radiation; I was studying various kinds of responses.

Mr. WALKER. To radiation?

Dr. LUSHBAUGH. To radiation, yes. And so in this situation I had no interest in the efficacies of drugs against radiation sickness, so I wasn't using children.

Mr. WALKER. So with regard to your studies you would have always had as a factor in your decision that any extrapolation of data from those kinds of ongoing treatments of adolescents would have been of no use to you in your final analysis. Is that a correct——

Dr. **Lushbaugh**. Not only that, but as a matter of fact, the analyses that we made, and we had incorporated in this book "Radiobiological Factors in Manned Space Flight," those were the large doses, and where we got these large doses from all over the country. We had finished up that part of the study, and so a patient like Duane Sexton, getting 350 roentgens, I believe he was the last one to be so irradiated at that dose, and he was irradiated 1½ years after the NASA book was published and in print. So I had no way to use Duane Sexton's data.

Mr. **Walker**. The bottom line on this is that in terms of the Sexton boy, there was no reason for NASA to put pressure on anybody to in any way take data from that particular treatment and utilize it in any of the work that it was doing.

Dr. **Lushbaugh**. That is right.

Mr. **Walker**. And Dr. Vodopick, you were never under any kind of pressure from NASA in terms of the treatment, and you don't have any knowledge that NASA ever used any data from the treatment that you gave to the Sexton boy for purposes of its analysis?

Dr. **Vodopick**. No; as far as I know, none of that data was ever used for NASA.

Mr. **Walker**. Thank you, Mr. Chairman.

Mr. **Gore**. Now on one of the funding proposals, schedule 19, dated October 23, 1969—and we have provided you with copies of these documents—you say on page 20 of that proposal that you discuss active canvassing program for increasing our utilization of these facilities. And you say—

> The prospective human radiation sensitivity studies will be continued at least at their present level in the LETBI facility and will be increased in number in both LETBI and METBI.

And this is you asking NASA for continued funding:

> As more patients appropriate to this type of therapy are referred to us by our consultants, an active canvassing program for increasing our utilization of these facilities has been developed using the mail, semi-popular medical news releases, scientific journals and formal talks at scientific and medical meetings. We anticipate that this program will produce a greater influx of patients than we have experienced in the last 2 years.

Now, first of all, did you embark upon this active canvassing program to try to——

Dr. **Lushbaugh**. I didn't, but Dr. Andrews and Dr. Edwards did. That had to be a clinical-type of thing where there had to be patient reports, reports of the efficacies of the various kinds of therapy. They had to give talks at various meetings, State medical meetings, local meetings, this sort of thing; and to my knowledge, they did do some of these things but I didn't and as you can see from my charts, it didn't pay off. There was no great increase in patient load. You see, there were many doctors in that area of Tennessee who had previously referred patients into ORAU who now, with the growth of chemotherapy, no longer had to do this. We also had a competing hospital at the University of Tennessee where a chemotherapy oncology group was coming up, and so that competition was rising. And what I said in that proposal did get underway at a Dr. Andrews/Dr. Edwards level, but I didn't go out and try to compete. I wouldn't have known anybody in the area that I would be able to call up and say, "Hey, Joe, send us some patients." I didn't have that kind of relationship—and I still don't—with physicians in east Tennessee.

Mr. GORE. I want to come right back to this, but I want to recognize you, Dr. Comas. We are going to depart from our normal procedure and excuse you from the witness table because of your personal schedule. Did you want to make a comment before you left?

Dr. COMAS. Yes, Mr. Chairman, I would. I would like to reiterate this point that has been asked so many times in the course of these proceedings about whether or not we were influenced by NASA in any way in the selection of patients to receive that kind of treatment. And my comment to it is that we were not influenced in any way. I personally never met a NASA person, never did. I never had any correspondence of any kind with anybody associated with it.

This was done through the administrative structure of ORAU. It would seem inconceivable to me that any one of us would have opted to do such a thing. It is hard to convey, so many years afterwards, the feeling of the group. This was a group of physicians who were there, interested in trying to find ways to deal with these diseases more effectively than it had been the case up to then, and our interest was a medical interest. Now, there was some spinoff from it, because when people get irradiated they develop some things like some get nauseated, some vomit, and some get tired, et cetera. NASA wanted the spinoff. I didn't see anything wrong with it then, and I don't see anything wrong with it now.

I would like to be able to prove such a contention. I cannot, I just can tell you that we did not do it. We were not influenced by NASA in any way. In fact, the patients I irradiated, I think, that for the most part I had not the faintest idea whether they were in the NASA study or they were not.

Mr. GORE. All right, very well. Thank you very much. Thank you for appearing here today.

Dr. COMAS. Thank you.

Mr. GORE. Now, Dr. Lushbaugh, in the same proposal for funding, the posttherapeutic benefits of low dose rates are discussed, and it goes on to say, "The need is more acute than ever for data derived directly by observation of man's reaction rather than assumed from animal studies."

Did this acute need for data change the treatment any patient received? The same question.

Dr. LUSHBAUGH. I don't believe it did. I mean the need that I had for data like that did not, but the statement that that was based on actually comes out from the space radiation study panel's book where, as a result of the retrospective studies on patients, some of those retrospective studies showed that small fractionated doses in those patients did produce good therapeutic results, and also showed that some of the patients were able to stand fantastically large doses over long periods of time, in the order of 1,700, 1,800 rads over maybe 5 or 6 years, where the doses worked.

This was of great interest to NASA, because it would mean the long space flights and the like in small radiation fields an astronaut could conceivably accumulate small doses at multiple intervals over a long period of time, and so this was what was being said there. And as some of the space flights began to occur, and I don't have them in context with me, it became obvious that the possibility of a huge dose of radiation in space to an astronaut was probably very small, and dependent on the 11 years' Sun cycle. The possibility of getting small radiation doses in astronauts repeatedly, because they were used over and over again—every time they went through the South Atlantic anomaly, they went through the Van Allen Belt, and got some radiation. But when you look back at the record of what happened there, you found out that a lot of this was a tempest in a teapot because astronaut doses was actually about 0.6 rads per mission or something of the sort, way down in dose levels where we are unable to detect any kind of physiological responses at all.

Mr. GORE. Well, as that became more apparent to NASA, the interest in lower and lower doses increased, correct?

Dr. LUSHBAUGH. Yes.

Mr. GORE. And you became interested in lower and lower doses and the effects thereof, correct?

Dr. LUSHBAUGH. And simultaneously with that, the staff that was observing that, found that 30 roentgens a day was an effective therapeutic dose. At that point in time, instead of putting their patients in the LETBI facility, they began putting their patients in the METBI facility and doing what was very attractive clinically, which was irradiating their patients on this outpatient basis, which worked very well. The patients like it, because they were able to come in, get irradiated and go back to work.

Mr. GORE. Well, now on the schedule 19 for fiscal year 1972 you state—you talk about going down to the lower and lower doses, and on page 9 you state: "The hematologic results of these small exposures were too short-lived to be considered therapeutic effects but were radiobiologically of great interest."

Dr. LUSHBAUGH. I don't really recall what I am saying there. I don't recall my basis for that.

Mr. GORE. Yes.

Dr. LUSHBAUGH. I couldn't interpret that for you at this point.

[The information follows:]

Oak Ridge
Associated
Universities

Post Office Box [illegible]
Oak Ridge, Tennessee [illegible]

Medical and
Health Sciences
Division 615/576-3090

November 10, 1981

Mr. Albert Gore, Jr., Chairman
Subcommittee on Investigations and Oversight
Committee on Science and Technology
U. S. House of Representatives
Suite 2321
Rayburn House Office Building
Washington, DC 20515

Dear Congressman Gore:

In the September 23 hearing, I was asked an important question that I was unable to answer as precisely as I would have liked to have been able to. This question is stated on page 218 of the transcript of testimony sent to me for review last week. Since the hearing I have looked up the histories of the two patients who received radiation exposures that proved to be too small to have been beneficial to them. I find that the medical records in both cases show that their TBI treatments in the LETBI facility were shortened in order to accommodate their personal needs of the moment. In one case the man, a retired Baptist minister, had to stand in for the regular minister of his church who was called away unexpectedly. This man (Rev. Glass) was, therefore, only treated at night instead of all through the day and night as was routine. As a result his daily exposure amounted to about 10 R instead of 30 R as was usual. In retrospect, this daily dose proved to be insufficient to produce a remission and his treatment had to be repeated sooner than planned. In the case of the other man (Mr. Sloan), his treatment regimen was similarly altered to permit him to take care of his wife during a flare-up of her rheumatism. The small daily dose that resulted was found similarly to be insufficient. In my analyses of these cases, I concluded that these events showed that man, like other animals, could repair cellular effects of such small daily doses rapidly enough to make these slow dose rates more tolerable than the faster rate of exposure. This observation was not particularly a new discovery; it merely confirmed for human radiobiology that man had radiation repair capabilities as previously suggested from animal studies, and it provided a semi-quantitative measure of the repair rate.

My testimony goes on (on page 219) to say (rather poorly) that finding out that 10 R/day is not effective is also clinically important to know so the clinician can plan his dosage regimen more realistically.

Sincerely yours,

C. C. Lushbaugh, M.D., Chairman
Medical and Health Sciences Division

CCL:fb

Enclosure

Mr. GORE. Well, it is a provocative quotation, because at a time *when NASA was becoming more interested* in the smaller and smaller doses, a couple of outpatients were given smaller and smaller doses until it got down to a level where you say the results couldn't be considered therapeutic but they were radiobiologically of great interest. Now the inference one could draw from that is that in some fashion the doses selected for these two patients was selected in order to satisfy the need for that data which was becoming of greater value, in spite of the fact that it later was concluded that it didn't have any therapeutic value.

Dr. LUSHBAUGH. But it never was selected for the benefit of me or the NASA group. These lower doses were selected in order to find out how small a dose did you need clinically to produce the effects, and you had to go in the system down to someplace where you got to ineffective doses——

Mr. GORE. Why?

Dr. LUSHBAUGH. Yes. Because why give a person 30 roentgens in an outpatient visit if you can just give him 10. It is not that you are saving roentgens but you are saving time. And in our retrospective study there were patients who were fractionated exposures over time where they got 5 roentgens a day. There were an infinite number of kinds of patterns that were very difficult to analyze in retrospect. We tried to, and we continue to do that, but as I say, there were not a number of them that made it all worthwhile.

Mr. GORE. And you go on to say that—

> This clinical radiotherapeutic approach using increasing low exposure rates is now providing us with numerous retrospective observations of effects in exposure situations that are increasingly more relevant to the occupational medical needs of deep space exploration where exposures are expected to be small, multiple, and randomly timed.

I take it the interpretation you are placing on this document is that the dose rates were selected in order to establish the lower level of therapeutic effects, and when you went below it, you then determined it. But then you are saying to NASA this information is really interesting and is of value to your space program.

Dr. LUSHBAUGH. I am being a salesman.

Mr. GORE. OK, all right. I want to come back to this, but we have another vote that we simply have to go to on the floor. We will be back in about 8 or 9 minutes.

[Recess.]

Mr. GORE. The subcommittee will come back to order.

When we just broke for the vote, you said, Dr. Lushbaugh, that you were being a salesman. I take it by that you were putting the kind of interpretation on events that you felt would elicit a positive reaction from NASA and encourage NASA to continue providing money——

Dr. LUSHBAUGH. Yes.

Mr. GORE [continuing]. For the experiment?

Dr. LUSHBAUGH. Exactly so.

Mr. GORE. Again the question is whether that salesmanship in any way influenced the design of the clinical procedures?

Dr. LUSHBAUGH. I understand.

Mr. GORE. And your response is that it did not.

Dr. LUSHBAUGH. It did not, no.

Mr. GORE. Let me ask all of you about this 1974 AEC report. I know that is troubling to you. What reaction do you have to that?

Dr. LUSHBAUGH. Well, my reaction is that Dr. Bibb's response, I think, is a very accurate one; that it is a strongly stated statement of conditions which are seen through the eyes of a committee that had as I think one of its goals to help AEC, to make a decision about whether or not we were going to get a new hospital or not. Dr. Andrews' contention, was that the medical division needed a new hospital, and as Dr. Bibb explained, he was making a proposal that this was needed, and so a review was done. And this was the review that was done of the program, seeing whether or not the program would support such a new hospital and be a rational basis for it.

Mr. GORE. All right.

Dr. Hubner, with respect to the human use committee, you were a member of that for some time.

Dr. HUBNER. I became a member of the human use committee in 1976. I had not been a member of that committee before that time.

Mr. GORE. Oh, I see. All right.

Dr. HUBNER. I am still a member of the committee, and in that role I have reviewed the guidelines and procedures that the committee need during the years.

Mr. GORE. Is it true that the initial determination of whether or not patients were at risk was made by the medical division and only those patients so designated were referred to the committee on human use?

Dr. HUBNER. According to today's procedures, the senior investigators, if they have an idea for a clinical investigation, have to write up a proposal which clearly states the objectives of the study, how it is going to be done, what parts of the studies or the substances and procedures used are considered risky, what the risks are, how many patients will be studied, what the expected endpoints are, and how you measure the endpoints. That proposal is then discussed by the committee. In fact, the proposal has to be in the hands of each committee member at least 2 weeks prior to voting on that particular proposal. The proposal is discussed among the members of the committee, either by telephone or in a meeting, and the investigators have to be available to answer questions if there is any concern about these proposals. Then the committee votes.

Mr. GORE. OK. Let me ask you about another matter, the high-exposure, total-body irradiation facility. Now this is yet a third radiation facility. This was used for large animal studies at the University of Tennessee-AEC Agricultural Research Laboratory. This facility had a maximum exposure rate potential of 50——

Dr. HUBNER. Fifty R per minute.

Mr. GORE. Fifty roentgens per minute?

Dr. HUBNER. That is correct.

Mr. GORE. What diseases require that amount of dose?

Dr. HUBNER. The high dose rate radiation facility at the "UT farm", was and still, is a very unique facility. Because of this enormously high dose rate, this facility was selected to be used to prepare patients for bone marrow transplantation. At that time, most investigative clinical investigation units involved in bone marrow transplantation used doses of 1,000 rad delivered at 5 or 5.7 R per minute in order to prepare the patients for bone marrow grafting. That is an extremely high dose and potentially dangerous if the graft fails.

Our reasoning for selecting the dose we used in our bone marrow transplantation patients was that we could reduce the dose, if we were able to use a high dose rate, and still achieve the same amount of immunosuppression. This assumption was based on experiments by Dr. Gengozian, who has clearly shown in animal experiments that you can give a lower dose of total-body radiation at a high dose rate, and get the same immunosuppressive effect as from a large dose delivered over a long period of time. So the investigators involved in this bone marrow transplant project felt sure that they could get sufficient immunosuppression with a lower dose but given at a high dose rate.

In order to avoid failure of the graft—and this is what some people argue—you have to have a high dose to get sufficient immunosuppression and acceptance of the graft. In order to avoid failure of the grafts, having committed ourselves to an exposure of 500 roentgens, we added to the preparative protocol eight daily injections of antithymocyte globulin, either horse or goat globulin, as additional immunosuppression. Four patients have been treated in that fashion, irradiated at this high dose rate facility, and then they were given bone marrow transplants.

Mr. GORE. This was a facility that normally irradiated cattle and horses?

Dr. HUBNER. Yes, that is correct; or other large farm animals.

Mr. GORE. But principally cattle and horses?

Dr. HUBNER. I don't know what the proportions were, but there were ponies, cattle, and swine, I think.

Mr. GORE. But on four occasions persons were irradiated there?

Dr. HUBNER. That is correct.

Mr. GORE. Was there a sanitation problem?

Dr. HUBNER. This was strongly considered by our clinical staff and the microbiology team. The facility was scrubbed clean prior to any patients entering the facility. In addition to that, the patient was transported from the Medical and Health Sciences Division Laminar Flow Unit where the patient had been for at least 10 days in a sterile environment prior to this total-body radiation. He had been transferred in a specially designed transfer stretcher, which had its own independent filtered air supply. In fact, he was in a life island, had no contact with the outside, and he was transported in that life island to the facility; irradiated without ever being touched by anybody or any air being able to get into this confined area; and was returned to the medical division and returned into the Laminar Air Flow Unit. The patients were extremely closely monitored for microbiological contamination afterwards, and they were clean when they came back; they were not infected or exposed to any infectious agent at this facility.

It was a unique facility; to my knowledge, the only one available in those days. And as it turns out in today's procedures, the tendency is to lower the total body radiation dose for bone marrow transplant patients but give it at a higher rate. M. D. Anderson Hospital is now going to 26 roentgens per minute and lowered their dose to 760 rads or so. And if more centers had the capability to use higher dose rates, I think the doses would come down too.

Mr. GORE. OK. No patients have been irradiated since 1975; is that correct—since 1974?

Dr. HUBNER. That is right. We had one bone marrow graft, a patient in 1970, one in 1971, one in 1972, and one in 1973. That was the last one, in 1973.

Mr. GORE. And at the medical division as a whole, there have been no patients irradiated since——

Dr. HUBNER. Since 1974.

Mr. GORE. Since 1974. You have reviewed the consent forms?

Dr. HUBNER. Right.

Mr. GORE. Is that correct?

Dr. HUBNER. That is right.

Mr. GORE. What is your judgment on the adequacies of the consent forms used during this period?

Dr. HUBNER. I think they were perfectly adequate, the consent forms used for these patients in the early days and especially since the 1970's when this issue about informed and fully informed consent was becoming more and more actual. The FDA in 1975 has come out with a number of new regulations and guidelines concerning the question of informed consent. And I think the debate is not over yet, and we continuously have to reveiw and revise our committee guidelines and consent forms almost every 2 to 3 years.

Mr. GORE. Now were patients informed that data from the irradiation experience would be used in the ongoing study for NASA?

Dr. HUBNER. It was not in the consent forms I have seen for LETBI or METBI irradiation. I did not see any indication of NASA of any kind. And as was said earlier in this testimony, informed consent was obtained by the chief of clinical services, who was the one who would discuss the type of treatment, the dose, and the risk with the patient. And he would have been the one to discuss the question whether any data and observations collected would be made available to NASA, and I don't know to what extent that took place.

Mr. GORE. Now, Ms. Sipe, you have said on many occasions that you told patients that NASA was interested in some of this data. Is that correct?

Ms. SIPE. Right.

Mr. GORE. But that was just on an informal basis?

Ms. SIPE. Yes.

Mr. GORE. And we will hear from some patients shortly. Now, were the patients free to leave the study at any time, Dr. Hubner?

Dr. HUBNER. Yes; that is right, at any time.

Mr. GORE. Were the possible benefits of alternative treatments explained to the patient?

Dr. HUBNER. I am sure they were.

Mr. GORE. But you don't know who did so.

Dr. HUBNER. I personally never had any involvement with the LETBI patients.

Mr. GORE. Dr. Vodopick, was that a common procedure, to explain the benefits, possible benefits of alternative treatment?

Dr. VODOPICK. I think this was mainly done by Dr. Edwards, and I don't recall what he discussed with the patients when this was done.

Mr. GORE. OK.

Dr. LUSHBAUGH. Dr. Edwards shows in his notes, however, that—he says, "I did that."

Mr. GORE. Pardon me?

Dr. LUSHBAUGH. I think in the notes, nursing notes and the other notes in the history, you will find a note by Dr. Edwards that says that he did discuss with the patient other alternate forms of treatment.

Mr. GORE. Dr. Hubner, what is your opinion of the placement of the animal cages behind the LETBI facility?

Dr. HUBNER. I don't see any big problems with that kind of practice. Of course it is not ideal. If we had facilities or if we could afford separate facilities for human patients and animal experiments, that would be fine. But having an isolated area in the outer shell of the LETBI facility shielded and protected by plastic walls and with a separate air exhaust system in that overall patient facility, with extreme care of the investigators taking care of the animals—it is my understanding that the ordinary animal caretakers did not take care of the animals, but rather the senior technicians of the investigators took care of the animals and removed any garbage and old food, what have you—I don't see much wrong with that procedure. I think that was done quite responsibly and in the best way they could.

Mr. GORE. Now you have reviewed the protocols for these experiments. Are you satisfied that they were adequately designed and appropriate for the time period?

Dr. HUBNER. The protocols for the LETBI experiments?

Mr. GORE. Yes.

Dr. HUBNER. I haven't been able to find the very first written protocols for the LETBI treatments. I have seen a number of protocols written up in drafted papers for publication.

Mr. GORE. What about the protocol No. 10 for total body irradiation in patients with hematologic disorders? This was approved on September 18, 1969. Are you saying that there was no protocol for total-body irradiation before that date?

Dr. HUBNER. I couldn't find one that was submitted to a human use committee, because it didn't exist until 1967.

Mr. GORE. All right, fine.

Dr. LUSHBAUGH. Is that this one? Did you say September 18, 1969?

Mr. GORE. Yes.

Dr. HUBNER. This protocol identifying project No. 10 was written on this form which was adopted on April 4, 1967, and it looks like it was reviewed by the human use committee and approved on September 18, 1969.

[The information follows:]

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: C. Lowell Edwards Identifying No. 10

Project Title: Studies of Total-Body Irradiation in Patients with Hematologic Disorders

Comments:

The committee approved this project but recommended the purchase of new dosimetry equipment for the METBI facility to allow continuous monitoring.

Approved: Sept 12, '69 (date)

Disapproved: ________ (date)

Robert D. Lange, M.D.
Secretary, Committee on Human Studies

Still active (11 Dec. 73)

Cancelled June 25, 1975 (See attached report)

REVIEW AND ACTION

Committee on Human Studies

Oak Ridge Associated Universities

Medical Division

Principal Investigator: Nazareth Gengozian Identifying No. _______

Project Title: Therapeutic Allogeneic Transplantation of Human Bone Marrow

Marrow

Comments:

The committee approves the project as submitted contingent on the preparation of a release which meets all legal requirements. The committee further recommends that an independent evaluation of the extent of understanding of the release on the part of the patient or parent be made if feasible. It is suggested that a member of the clergy might make such an evaluation. The committee also expressed a wish that they be kept informed on the progress of this project.

Approved: Jan. 19, 1970 (date)

Disapproved: __________ (date)

x Robert D Lange M.D.
Secretary, Committee on Human Studies

Jan 25, 1975 Canceled (See minutes)

Adopted 4-67

Committee on Human Studies Page 1

Oak Ridge Associated Universities

Medical Division

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

(Three copies required. Use reverse side of these forms if additional space is needed.)

Date 9-18-69

I. Senior Investigator: C. L. Edwards

Co-Investigators: C. C. Lushbaugh, Helen Vodopick, Francis A. Goswitz, Bill Nelson, R. M. Kniseley, and G. A. Andrews

Title of Project: "Studies of Total-Body Irradiation in Patients with Hematologic Disorders"

II. Objectives of Experiment: (Use additional blank pages if needed.)

The objectives are (1) to develop better irradiation methods for therapy; (2) to improve methods for assessing and treating accidental gamma and neutron radiation injury; (3) coincidentally to collect and evaluate critically information potentially useful to NASA in dealing with high levels of occupational radiation exposures in space exploration; and (4) to devise new and more precise end-points that define the radiation dose response in man.

Certain selected chronic malignant diseases, particularly chronic leukemias and lymphoma, can be controlled effectively by total-body irradiation. More information is needed on how this treatment can best be applied. Also there is an urgent need to understand the clinical physiologic events that occur after total-body irradiation so that accidental and military exposures (or exposures in space exploration) can be most intelligently treated. Laboratory and clinical observations are made on patients irradiated for malignant disease, at the

Adopted 4-67

II. Objectives of Experiment:

medium-exposure-rate total-body facility (METBI) comprised of eight 300-curie ^{137}Cs sources providing a homogeneous irradiation field with a dose rate between 1 and 4 R/min. The low-exposure total-body irradiator (LETBI) is also in operation and at present provides exposures of 1 to 5 R/hr in a homogeneous field of gamma radiation provided by 10 cobalt-60 sources.

The experimental high-dose-rate unit at UT-AEC provides 50-75 R/min exposures from ^{60}Co sources.

The study will emphasize:

1. Precise measurements of irradiation dose and dose rate.
2. Frequent blood counts and bone-marrow examinations at specified days to permit comparison between patients and groups of patients.
3. Careful monitoring of symptoms and biochemical changes which may indicate physiologic effects of irradiation.
4. A comparison of different doses, dose rates, and protracted versus fractionated doses as to therapeutic effect, symptoms produced, hematologic and biochemical responses.

III. Methods of Procedure:

Brief description of methods, all medications including name and dose range, number and types of subjects anticipated, time for single session, total number of sessions, total duration of study, methods used to screen subjects, etc. (Use additional blank pages if needed.)

A. Selection of Patients.

Patients will be selected from among the patient population as referred to the Medical Division. The selection will not be randomized but only patients meeting the following criteria as to diagnosis and manifestations of their disease will be selected.

Diagnoses:	Manifestations:
1. Polycythemia vera	1. Thrombocytosis
2. Chronic granulocytic leukemia	2. Leukocytosis
3. Chronic lymphocytic leukemia	3. Symptomatic lymphadenopathy, non-hemolytic anemia without thrombocytopenia
4. Lymphosarcoma	4. Bone-marrow invasion plus those in #3 above.

Some of these patients will be exposed to 100-250 R total-body irradiation in the LETBI (1.5 R/hr) facility or by fractionated daily doses of 30 R/day in the METBI (1.5 R/min) facility. Others will be treated with 50-100 R exposure in the METBI facility.

Each patient will be followed with frequent blood counts, cultures, and chemistry determinations prior to, during, and for a period of at least 6 weeks after exposure (sample protocol for METBI, 100 R; LETBI, 250 R; METBI, 150 R fractionated, enclosed). During this time he will receive no other specific therapy unless, (1) he was being maintained on some chemotherapy prior to and during the pretreatment period, e.g. prednisone; (2) his condition is judged to be deteriorating after treatment without hope of response to the irradiation and it is the concensus of the clinical staff that some other form of treatment is indicated.

Therapeutic benefit will be assessed on the basis of:

Diagnosis:	Criteria:
1. Polycythemia	1. Return of the platelet count to normal 2. Relief of symptoms, such as pruritis
2. Chronic granulocytic leukemia	1. Return of RBC to normal 2. Reduced cellularity of bone marrow to normal 3. Reduction in splenomegaly 4. Relief of symptoms, general malaise, etc.
3. Chronic lymphocytic leukemia	1. Reduction in size of lymph nodes 2. Improved RBC values 3. Reduction in splenomegaly 4. Improved symptoms, e.g. reduction in discomfort, improved sense of well being
4. Lymphosarcoma	1. Reduction in tumor and organomegaly 2. Reduced bone marrow tumor 3. Improved RBC values 4. Improved symptoms

The therapeutic response to various radiation regimens will be compared with each other and with other methods of treatment.

III. Methods of Procedure (continuation page 2)

B. Radiation Protocols.

1. Single dose
   a. METBI - 50 R, 100 R at 1.5 R/min. Approximately 90 treatments have been given to about 75 patients. Only a few additional patients are planned for this series.

   b. LETBI - 50 - 250 R at 1.5 R/hr (up to about 9 days in the unit). Twenty patients treated. We hope to add about one patient a month for the next 3 years.

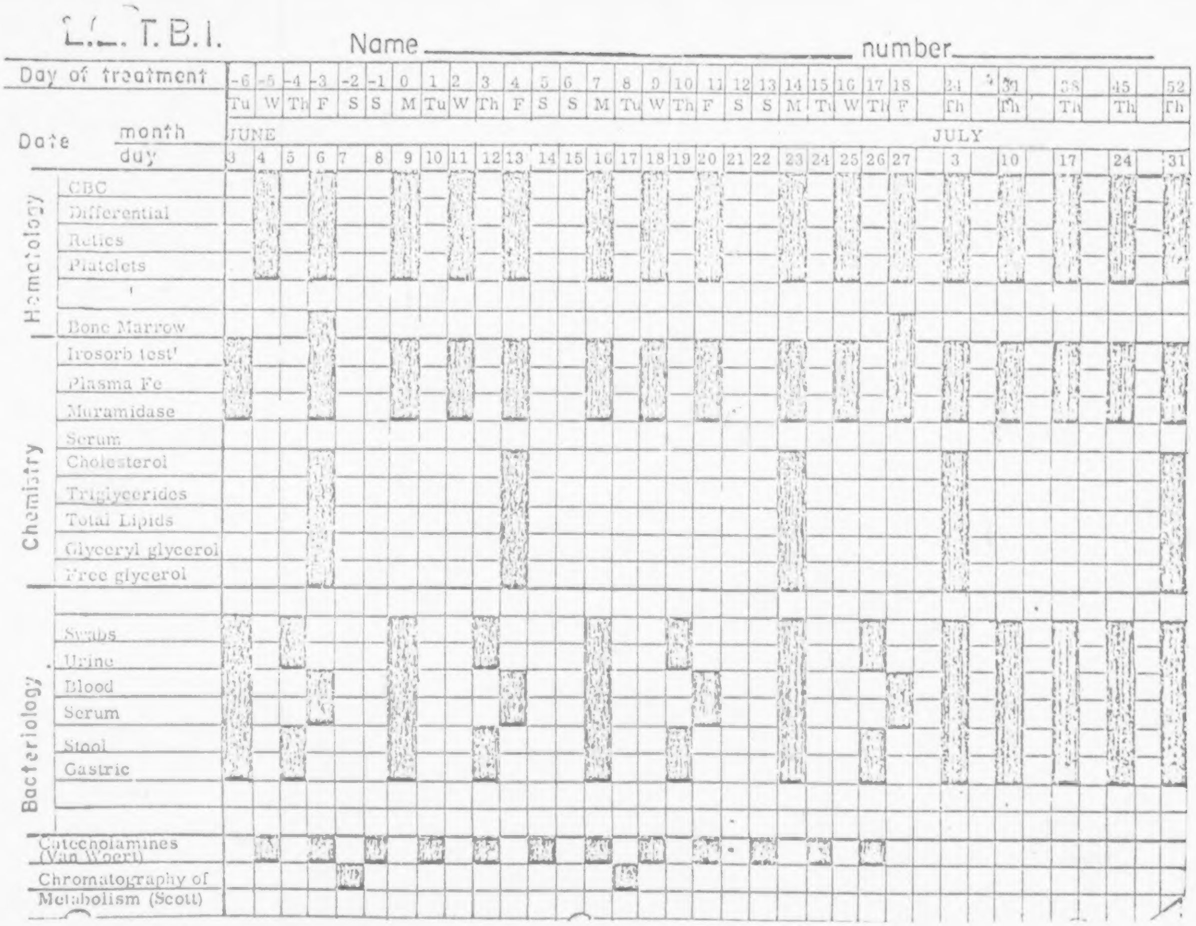
   c. UT-AEC High-Rate Irradiator - 50 - 100 R at 50 R/min. None treated till now. Objective: to determine dose-rate effect on the degree of response (compared to group A, B) in 8 cases of chronic granulocytic leukemia. Similar comparison may be possible in the other disease categories (5-10 patients/disease).

2. Fractionated Doses.
   a. METBI up to 250 R at 1.5 R/min with daily doses of approximately 30 R. Five patients treated. Objective: to add enough patients to make a valid comparison with the same total dose in LETBI protracted to the same time span.

   b. Repeated low-dose maintenance exposures in METBI or LETBI (weekly or monthly doses in the 10 - 30 R range). None treated. Numbers to be included in the series depends on availability of patients and results of early studies. Five to ten patients in each disease category would be desirable.

III.

C. Laboratory Studies (see copy attached protocol).



L.L. T.B.I. Name ______________________ number ______________

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Chromatography of Metabolism (Scott)						▨										▨																				

Studies of Total-Body Irradiation in Patients with Hematologic Disorders

Application for use of humans as experimental subjects Page 2

IV. Responsibility of Senior Investigator:

The principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date: Ongoing

Signatures: C. Lowell Edwards, M.D. Investigator
Investigator
Helen Vodopick M.D. Investigator
Francis A. Goswitz Investigator
Bill M. Nelson
Ralph M. Kniseley
Gould Andrews

MEDICAL DIVISION REVIEW:

The application described above has been reviewed and approved.

Gould Andrews Chairman

Date: 18 Sept 69

Revised October 1969

IV. Possible hazards and their evaluation

We have considered the following possible hazards:

1. Overdose of radiation due to technical failure. Both the LETBI and METBI facilities are especially designed to eliminate any possible defect in position of sources that might alter the dose. Extensive dosimetry is done with each exposure in both facilities. Before the high-dose-rate exposure field at UT-AEC is used we will plan carefully, with our radiation safety staff, methods of eliminating any possibility of accidental overexposure there.

2. Electrical shock during exposure. Because of the physiologic monitoring during the prolonged LETBI exposure we have considered the possibility of electrical shock to the patient. The monitoring device includes an electrode to the patient's chest that is grounded. If a short should occur in any improperly grounded electrical device operated by the patient, a fatal shock could occur. To protect against this, isolation transformers have been put in for the two lamps and television set operated by the patient. A further study is being undertaken to check on the grounding of the light fixtures in the room, and particularly of a dimming device for overhead lights which the patient sometimes operates.

3. Excessive depression of normal marrow elements after irradiation. Careful assessment of the patients' hematologic status is made before treatment is given. Patient selection and choice of radiation dose are carefully planned to reduce this hazard. A number of patients with diseases falling in the appropriate categories are eliminated because of low platelet counts or other evidences of inadequate marrow reserve. If patients do develop severe marrow depression we are prepared to give a protected environment and supportive therapy, including platelet transfusions and antibiotics based upon extensive bacteriologic studies directed by Dr. Balish.

4. Less than optimal long-term results. We are aware, we believe, of the various controversies over the treatment of these diseases and we try to select patients in line with our best judgement so as not to deprive them of benefits at least equal to "standard" therapy.

   In polycythemia vera, the evidence of Modan that ^{32}P causes an increased incidence of acute leukemia has not been entirely accepted. We are cognizant of the deliberations of the polycythemia study group under Dr. Louis Wasserman and are prepared to modify our plan, or eliminate this group of patients if this appears indicated.

In chronic granulocytic leukemia the report of D.A.G. Galton, et al, indicates that patients given splenic irradiation and a variety of other types of external radiation develop earlier blast cell transformations than patients treated with busulfan. E. E. Osgood, on the basis of a very careful long-term study, finds that carefully titrated doses of ^{32}P give results better than any other form of reported treatment. Our past use of total-body irradiation may not be as good since it is not as well titrated as Osgood's ^{32}P. We are conscious also of the problems of busulfan including a significant incidence of early over-treatment and certain peculiar late metabolic complications.

In chronic lymphocytic leukemia there is a good deal of difference of opinion about the value of suppressive therapy, with many hematologists tending to believe that in patients who are tolerating the disease well, the less therapy the better. We recognize the possible validity of this viewpoint and adopt it with some patients, excluding them from the total-body radiation ~~trials.~~ series.

V. Radioisotopes and New Drugs:

If the study involves radioisotopes, indicate action of the ORAU Medical Division Isotope Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

Therapeutic Allogeneic Transplantation of Human Bone Marrow

Application for use of humans as experimental subjects

V. Responsibility of Senior Investigator:

The principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date: Feb 1970

Signatures:
Investigator
C. Lowell Edwards Investigator
Helen Vodopick M.D. Investigator
Karl F. Hubner Investigator

MEDICAL DIVISION REVIEW:

The application described above has been reviewed and approved.

Gould Andrews Chairman

Date: Jan 19, 1970

Revised October 1969

VI. Responsibility of Senior Investigator:

The principal investigator will follow the procedures of the ORAU Medical Division Committee on Human Studies in obtaining "informed consent" from the subject under study. The investigator recognizes that he retains the primary responsibility for safeguarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of Committee on Human Studies.

Starting Date Continuing

Signatures: ______________________
Investigator

____
Investigator

____
Investigator

MEDICAL DIVISION REVIEW

VII. The application described above has been subjected to review and has been approved.

____
Chairman

____
Date

No. 10 Studies of TBI in Patients with Hematologic Disorders

With the closing of the clinical facility, the therapeutic total-body irradiation project was discontinued after a total of 194 patients received exposures of [illegible] R to 250 R in METBI or LETBI. See 1973 Research Report OR[illegible]23, page 5, and an updated Table 1. These patients are no longer being followed at ORAU. The data are being compiled for publication.

Mr. **Gore**. Dr. Vodopick, did you explain to Mrs. Sexton the possible benefits of alternatives in his case?

Dr. **Vodopick**. I am sorry, alternative benefits?

Mr. **Gore**. Possible benefit of alternative courses of treatment.

Dr. **Vodopick**. Initially?

Mr. **Gore**. Yes.

Dr. **Vodopick**. I didn't talk to her initially. That was Dr. Edwards who talked to her initially.

Mr. **Gore**. But you did talk to her right before the total-body irradiation?

Dr. **Vodopick**. No; I believe that was Dr. Edwards. There is a note in the chart that Dr. Edwards——

Mr. **Gore**. There is a note on that chart?

Dr. **Vodopick**. Yes.

Mr. **Gore**. But there is not one with respect to the first.

Dr. **Vodopick**. Well, there is a special drafted consent form which is submitted with the testimony.

Mr. **Gore**. We have already put that in the record.

Dr. **Vodopick**. Right.

Mr. **Gore**. OK.

Dr. **Vodopick**. And he went into it, I am sure, with her at that time.

Mr. **Gore**. Okay. Now one other thing, Dr. Lushbaugh. You had a relationship with NASA which antedated your arrival at Oak Ridge; is that correct?

Dr. **Lushbaugh**. No, sir.

Mr. **Gore**. I thought that you started work on the book——

Dr. **Lushbaugh**. We started the work on the book after, as far as I was concerned, after I got to Oak Ridge. I arrived in Oak Ridge in September of 1963, and I don't recall exactly when I became a member of the Space Radiation Study Panel, but I know that when I was put on it, Dr. Andrews was made a consultant to it, and Dr. Wright Langham, who was the leader of the Space Panel, he was my Los Alamos superior. But I don't really recall exactly when that was, but it was, I think, shortly after I went to Oak Ridge.

Mr. **Gore**. All right, I think I have just about exhausted the questions that we have here, and I apologize to all of the people who have been waiting to testify. I would like to thank all of you for coming and helping us in this inquiry.

I take it that none of you would have objections if we submit additional questions in writing for the record. I don't anticipate a great many of those. You wouldn't have any problem with that, would you?

Do any of you have anything to say before we go to the next panel?

Dr. Vodopick?

Dr. **Vodopick**. If I could just add to this question about canvassing.

Mr. **Gore**. Yes.

Dr. **Vodopick**. I think that is a procedure that is not too unusual for institutions that are trying to gather research information. I know it is done by NIH, because I frequently get letters stating that they would like patients with ovarian cancer or leukemia or such. It is not with the intent of soliciting these patients. It is letting the doctors know that you are interested in these particular types of diseases so that, if they see fit to send their patients to these institutions, they know there is a program that is actively investigating these particular diseases. So I do not think that was unusual at all at the time, and it is still being done.

Mr. GORE. Very well. Thank you all very much for coming here today.

I would like to call our last panel consisting of two cancer experts, Dr. Robert H. Wiernik, director, Baltimore Cancer Research Center, University of Maryland Hospital, and Dr. Eli Glatstein, chief, Radiation Oncology Branch, National Cancer Institute.

Mr. GORE. Dr. Eli Glatstein, Chief, Radiation Oncology Branch, National Cancer Institute.

Gentlemen, I apologize for the subcommittee using so much of your valuable time. We have three witnesses who are coming right after you and I apologize to you.

We have a vote which promises to be the last for a while. It is important legislation out of the Intelligence Committee upon which I also serve and it is imperative that I go to that. I anticipate a break of no more than 8 minutes and I will be right back.

[Brief recess for vote.]

Mr. GORE. This subcommittee will come back to order. Dr. Wiernik, we will begin with you. Neither of you have prepared statements. You have been associated with an analysis of this since it first became public. People have asked you questions about what you thought about it.

Dr. PETER WIERNIK. I had your first name wrong before. After hearing the comments of the panelists here today and particularly those from the OARU Medical Division, would you please comment on the following questions. Were the TBI experiments performed by ORAU Medical Divison appropriate for the time period?

Dr. WIERNIK. That is a difficult question to answer. I am not a radiotherapist but I will answer from the standpoint of an oncologist in general.

I think the treatment status of acute leukemia in 1966, 1967, 1968 was such that any new approach was warranted in a clearly defined research setting. Whether or not it was appropriate to treat one or two or three patients a year with the hope of gaining any data from the experimentation is another question.

Mr. GORE. Dr. Glatstein.

Dr. GLATSTEIN. Before I answer I want to make one comment. That is I wish to make it clear I am here on my own. I have taken a day's leave from my job as the Chief of Radiation, Oncology Branch, at the Cancer Institute and in no way do I represent the Cancer Institute structure.

I think that the issue of the total body radiation as an investigative tool in the treatment of leukemia—I think it is a reasonable thing to have started in the 1960's. I think the goals were laudatory. I think many things took place during the 1960's, particularly the latter part of the 1960's, which basically eclipsed the importance of that question.

I think by the end of the 1960's it was pretty clear that was not an appropriate thing to do any longer.

There were other ways to go. Using radiation as a tool I think it was reasonable to start out that way but as Dr. Wiernik stated you need a critical mass of patients and you need a pretty hardnosed attitude about what it is you are doing, clearly defined goals, and a clearly defined means of assessing what the treatments are doing. I think there is some problem on that score.

Mr. GORE. What do you think the problems were on that score?

Dr. GLATSTEIN. The protocols which I have seen here don't seem to have a clear goal in terms of how treatment is going to be assessed. We heard a statement earlier that there was no intention of assessing the total body radiation as a sole means of treatment. Well, you can't have a protocol to assess total body radiation and then say you are not interested in that as a sole means of treatment. If you are going to look at it, you have to look at it in a fairly straight fashion.

Ultimately if there were any merit I think you would want to compare it to other forms of treatment and let the chips fall where they may. As best I can tell there is exposure. They failed to see if the dose got smaller and so forth, and they then switched to chemotherapy. I don't see what kind of usefulness that honestly gives although I think there was interest in the time in the 1960's of assessing whether radiation could in fact make any of the disease go away at all. However, by the experiments, clinical investigations from several different sources, specifically Saint Jude, I think by the end of the 1960's it was quite clear there were other ways of going and effective ways.

Mr. GORE. What would be the standard therapy for patients with malignant lymphoma, chronic lymphocytic and granulocytic leukemias, and polycythemia rubra vera during the time period in question?

Dr. WIERNIK. I don't know that there was one standard treatment. I think most patients with chronic lymphocytic leukemia around the country at that time would have been treated with oral medications. However, radiotherapy has always been used in the treatment of this disease and today is preferred by some therapists. In terms of leukemias, myelecytic leukemia in the early 1960's—and Dr. Glatstein can correct me if I am wrong—radiotherapy and oral anticancer drugs were equally used and there was a British study some time in the early 1960's that compared the two treatments in fact and found very little difference between them but does suggest the drugs might be more reasonable but that was standard radiotherapy rather than this kind of radiotherapy.

I don't have any quarrel with attempting to define the role of this kind of radiotherapy in chronic myelocytic leukemia in that particular time period. In terms of lymphomas I think that most patients received combinations of chemitherapeutic agents, one or two drugs at least, sometimes three drugs.

Although many investigators and many therapists in the field were using radiation in one way or another—not these kinds of doses—this was clearly experimental—but again I think the question of whether or not this would represent an advance in treatment—and clearly treatment needed to be advanced in those days—was a legitimate question.

My quarrel if I have any quarrel with all of this is one of quality rather than quantity. I don't see any great deviation from normal scientific activity here or from good clinical practice except perhaps that sometimes the range of normal activity is almost exceeded in some ways.

Mr. **Gore**. Dr. Glatstein, did you want to respond?

Dr. **Glatstein**. When you read various of the papers many of the papers that come from the Oak Ridge group—and I have read several of them—there is a goodly amount of information concerning the immediate response to treatment, blood counts, immunological grammars and so forth but as a treating doctor—which is what I am—I want to say something about the outcome of the disease itself and the outcome of the treatment.

If someone gets a complete remission of this disease I want to know how long it lasts. The thing that makes oncology somewhat unique in medical investigations is the obsession with time, to see how people do—not over a few weeks, not over a few months, but over years—and without really having any information on the outcome, I find that the papers that have been written are interesting in terms of acute radiation effects but really don't have any substance in terms of oncologic practice.

So that there is some value in these papers. There is no question. But in terms of cancer management I don't find much of an interest or value from that point of view.

Mr. **Gore**. What about the irradiation of animals in the space behind the LETBI facility. Do you have an opinion?

Dr. **Wiernik**. I would have to see the facility to have a legitimate opinion but it seems to me what I heard today is that every precaution was taken so there was no exposure of the patient to potential contamination from the animal material.

I myself would not have liked to have seen the setup as it was described. I think there is a potential for contamination and it alarms me that the potential even exists.

I certainly would have wanted to survey the treatment area prior to the admission of any new patient and I don't know that that was not done, but I think certainly it was something I would have wanted to do myself if I had had to treat a patient in such a circumstance.

Dr. **Glatstein**. My chief objection would be esthetic rather than objective.

Mr. **Gore**. What about the alternating use of the METBI facility for animals and then humans. Then animals again.

Dr. **Glatstein**. The same reservations with that also. If one is forced—under those circumstances he has to be extraordinarily careful with respect to microbiologic surveillance.

Mr. **Gore**. They said it was cleaned each time afterwards.

Dr. **Wiernik**. I think it should be stated it is not unheard of today to do that sort of thing. In that period of time especially.

Mr. **Gore**. This may be an unfair question but based upon your review of the evidence and listening to the testimony today does it appear to you that NASA's involvement in any way altered the treatment given to patients?

Dr. **Wiernik**. My sources of information are the documents shown to me by Members of your staff, the article in "Mother

Jones Magazine" and the testimony I have heard today and I don't see in any of that material evidence that any patient decisions were based on input from NASA or a desirability to please NASA. I don't think there is anything wrong whatsoever with supplying data to somebody else who might be able to use it for another purpose. I think today we would be required and if not required we would more or less feel obligated anyway to tell a patient that some other individual or some other organization or some other group may derive some information from what is being done to a particular patient.

But I don't think that these investigators—and I would hasten to say I don't think any investigator that is still functioning—would modify a treatment for a patient because somebody else would like a given set of data.

I would like to make one point though—I think it was almost addressed here—that is that most of the funding for medical research in this country is really study oriented rather than institutionally oriented. I think as you have been discussing all day that is a potential problem. If you have funding to do a study, naturally you want to complete that study in real time and you want the funds that are allotted to that study to accrue to you in the period of time that you expected to have them accrue. Not personal funds but research funds. So naturally there is a tendency to make sure that studies that you have arranged to do either on a grant or contractual arrangement accrue patients as fast as possible.

I can't categorically say that that means that investigators who are granted and funded for such studies are biased or in fact make decisions that are not inappropriate, but I think the potential is there and I think it would be safer and better for us all if institutions were funded and not individual studies. If brains were underwritten rather than individual studies contracted or subsidized I think we would all be better off.

Mr. GORE. Dr. Glatstein, same question.

Dr. GLATSTEIN. I don't see any evidence that that was a factor in patient decisions.

Mr. GORE. Were the protocols—and both of you have had an opportunity to review the protocols at the request of the subcommittee—were the protocols in your opinion adequately designed and appropriate for the time period?

Dr. WIERNIK. I don't mean to hedge but that is a difficult question because I think there were certainly studies conducted by reputable investigators during that time for which very little was written on paper in the way of a protocol. On the other hand in the best investigative centers in the country clearly protocols better than these were committed to paper before a study was begun. I think there are some brief areas in some of these protocols that could very well have been elaborated on prior to initiating the study and prior to obtaining approval.

I have to assume most of the approval for this was based on oral presentations to the Human Studies Committee at Oak Ridge rather than what actually was presented in a document such as one of these protocols.

Again I don't think there is anything for that particular time that is clearly inappropriate but I can't help thinking that if this place would have been in a larger city or associated more closely with a large university, Vanderbilt, University of Tennessee or some place like that that we might not be having this discussion at the present time.

Mr. GORE. Dr. Glatstein.

Dr. GLATSTEIN. I think if you are talking about the early 60's I think this is probably fairly representative of protocols that were going on at that time. I think by the end of that decade however, I think they had become much more goal oriented.

Again, I go back to the theme of time. The obsession with time. Following patients on a regular basis, assessing a number of very specific parameters of their illness and scoring patients in terms of "has everything gone away or not?" I really don't see that kind of logic built into this study as the kind of a criteria for therapeutic benefit—which is on page 5 of the study, of total body radiation patients with hemorrhagic disorders.

There is some criteria listed. There is no obsession with time. When was that going to be? At the completion of treatment? What about 1 month later, 6 months later, 1 year later, et cetera.

So, I think by the end of that decade I believe this was probably not acceptable. But at the beginning I think it was so I think it becomes somewhat arbitrary.

Mr. GORE. So again that would be consistent with the view expressed by some earlier witnesses that during the early years they were ahead of the curve and during the later years they possibly were behind the curve.

Dr. GLATSTEIN. I not only agree with that, I think in my own personal reading of the material that came forth from Oak Ridge—I know in the early 1960's I read a lot of the material that came out of there and realistically by the first part of the 1970's I didn't pay much attention to what came out of Oak Ridge any more.

Mr. GORE. Were the patients fully informed?

Dr. GLATSTEIN. That is a very difficult question to answer if you were not really present in the room at the time the explanation was given.

Mr. GORE. I recognize that. Let me rephrase the question. Having looked at the consent forms, were the consent forms consistent with reasonable medical practice during the time period?

Dr. GLATSTEIN. I believe they were but in point of fact the most important aspect of informed consent is how the physician communicates to the patient in terms of talking his language because clearly the way these consent forms are written—and I suspect it is true of every institution in the country—it would not take a very experienced lawyer to show that the patient really does not understand the intracacies of what he is told.

If one uses three or four syllable words—and the consent form certainly hasn't—there is no question the average patient will not understand the subtleties of what is being explained to him.

I think it is up to the standards of the time but I think they are suboptimal and I think the whole key to communication of informed consent is just how it is put to the patient by the physician.

That is why I think it would almost have to be on tape to give you an honest answer to that question.

Dr. **Wiernik**. I think the consent forms are fine. The earlier ones were very sketchy but in fact during that period of time—let's just say I have heard there are places in the country who had no consent forms at that time and over time these consent forms improved so the last ones that I have seen from the early 1970's were consistent with other university oriented research project consent forms.

Mr. **Gore**. Now with regard to the treatment of children with leukemia, was the treatment of children with leukemia appropriate during that time period? I have a couple of specific questions about this but do you feel comfortable answering that broader question before I go into the specifics?

Dr. **Wiernik**. I would rather have a more specific question.

Mr. **Gore**. What was the appropriate therapy for acute childhood leukemia of the kind Dwayne Sexton had during the midsixties?

Dr. **Wiernik**. Someone quoted a figure from the American Cancer Society earlier that indicated in 1966, 40 percent of children survived 1 year.

Dr. Glatstein and I looked at each other and shook our heads and said, "That is awfully low." The reason that is low is because the American Cancer Society figures are broad based and involve all sorts of situations throughout the country. Most patients with ALL in 1966 received less than adequate treatment. Those that came to university centers or to places that were involved in research in leukemia usually received two drugs, vincristine and prednisone or mathotrexate. They usually received this treatment virtually as soon as the diagnosis was made.

Usually within 3 to 4 weeks there was some significant evidence of improvement and 85 to 95 percent of patients under those circumstances would achieve a complete remission of their disease.

In that kind of a setting, I am sure that the median survival of a disease was far in excess of 1 year or 1½ years in 1966. Clearly some of the studies that were being done in 1966 and 1967 led to remarkable improvement in the outcome of treatment for that disease. Studies that were begun in several places, St. Jude's, National Cancer Institute, our place, others, led to 3½ year median survivals of that disease in children with a small fraction of children who were cured. So, I think the answer is yes and no. I think the treatment was probably better than what most children with ALL were receiving around the country at that time but I don't think it was as likely to be as effective as treatment in a number of centers around the country.

The one treatment issue that I would quarrel with with respect to the Sexton boy is that I really don't believe that it was appropriate to withhold maintenance of chemotherapy in that child in order to perform the study. I especially don't think it was appropriate to do that if it was not clear that that study could be done prospectively with a statistically potentially significant group of patients in a reasonable period of time. I don't mean to hedge but I think the answer is yes and no.

Mr. **Gore**. Now you have examined that medical record in some detail.

Dr. **Wiernik**. The Sexton boy?

Mr. **Gore**. Yes.

Dr. **Wiernik**. Yes, sir.

Mr. **Gore**. Dr. Glatstein, do you want to comment?

Dr. **Glatstein**. I would only add that in some of those relapse several times, particularly in the midsixties, there was no prognosis. I am not sure treatment was even indicated. It is hard to tell without actually ever seeing the kid. But realistically, I am not afraid to run up the white flag, myself. I may withhold treatment for patients if there is nothing good to offer and I know it.

Mr. **Gore**. All right, this is separate. These two are related but separate instances. The decision on TBI was after the four relapses, the immunotherapy procedure which included the withholding of maintenance therapy was before a relapse but during the first treatment of the disease, as I understand it?

Dr. **Wiernik**. Yes.

Mr. **Gore**. Dr. Glatstein, given the fact that there had not been a relapse, do you agree with Mr. Wiernik's conclusion that the withholding of maintenance therapy in order to better assess the results of the experimental——

Dr. **Glatstein**. It certainly wouldn't have been standard treatment.

Mr. **Gore**. All right. Now, to the 353-roentgen dose. After there had been four relapses and the standard chemotherapy agents had been exhausted, at that point was it appropriate to administer this total body irradiation?

Dr. **Wiernik**. I think so. I think that was a good proposed potential therapy. I think it was reasonable to study it. This is one of the few places that it could have been studied. I have no problem with that. The outlook for a child who has relapsed several times is uniformly fatal. This could have potentially worked. It was a good idea. It didn't work, but it was still a good idea.

Mr. **Gore**. Dr. Glatstein.

Dr. **Glatstein**. Without having seen the kid, I would agree on the principles. Again, I think if someone has elapsed several times, as I say, I don't feel compelled to treat them just because I know the prognosis is small. That is a philosophical point.

Mr. **Gore**. Yes.

Now just briefly to the immunotherapy procedure. Was it unreasonable to try?

Dr. **Wiernik**. I think the idea was a good one. I guess my frustration is it was such a good idea that it deserved better study. I don't know that there was adequate animal study information to go directly to humans, but let's assume that there was, because there was some data. The most important problem I have with it is that it should have been done first in patients who were in secondary remission.

Everybody knew in 1966, and everybody still agrees, that the most important thing that you can do for anybody with cancer, and especially a child with ALL, is to treat them properly the first time you get a crack at it. And the goal there is to certainly in a disease that was already known to be yielding to chemotherapy such as acute lymphocytic leukemia, the goal there would be first time around: certainly don't do anything that might impair the child's chances of being a long-term survivor.

When the child relapses and then if you are lucky enough to put the child back into remission, test the immunotherapy proposal at that point. I think we would be required to do it that way now. There would be no way without having some data in more advanced patients. I think that is appropriate. If you get a clue at all worth pursuing after studying advanced patients, then you can bring it up front into new patients as long as informed consent is obtained, but you really need that basic human data first before you can jeopardize standard treatment results.

Mr. GORE. Although people at Oak Ridge may not have been aware of it at the time, subsequent investigation has uncovered the fact that it had been tried with human beings in France, before it was tried at Oak Ridge. I believe that is correct.

Would you care to comment briefly on the bone marrow treatment program? Was the dose appropriate?

Dr. WIERNIK. I will let Dr. Glatstein.

Dr. GLATSTEIN. I am sorry, I am not sure if I know which part you are referring to.

Mr. GORE. This is not the Dwayne Sexton treatment, this is the——

Dr. GLATSTEIN. I have to look at the numbers again.

Mr. GORE. 500 roentgens.

Dr. GLATSTEIN. 500. I think as long as one is prepared to deal with the toxity of whole-body radiation in terms of bone marrow with some sort of supportive approach or transplantation, doses of 500 to 1,000 rads are used. Five hundred, in fact, is a little bit low by modern standard, by 1981 standard, it is a little lower for transplantation. However, I think, at this time now it is probably in the ballpark of what people were doing. I don't have any problem with that aspect.

Mr. GORE. Now, I think that completes the questions I have for this panel. Let me clarify one thing for the record. We asked the two of you to appear as expert witnesses, and we deeply appreciate the fact that you have taken the time to study up on this as much as you have. I would like to note for the record that, Dr. Wiernik, you were first made aware of this by Mother Jones magazine, is that correct, and you actually appeared at the press conference where the charges were first made as an expert selected more or less by the magazine; is that correct?

Dr. WIERNIK. However, they contacted me before the article was published and, after the article was published, asked me if I would attend the press conference he had arranged, and I did.

Mr. GORE. All right, fine. I note that for the record, to try to establish the objectivity of the two witnesses on this panel. And we appreciate the fact that you have taken out your whole day to listen to this and help us try to get to the bottom of it. Thank you very much.

Our final panel consists of former patients or relatives of former patients, Mrs. Farroll J. Burchfield, Mrs. Bonnie East, and Richard Sheldon. I would like to thank our three witnesses for waiting so long during the day. We appreciate it. Come on up to the witness table. If the three of you would raise your right hands and repeat after me: Do you swear the testimony you are about to give will be the truth, the whole truth and nothing but the truth, so help you God.

[Chorus of "I do."]

Mr. Gore. Thank you very much. Each of you has a prepared statement, I am advised, and since they are not very long why don't you just go ahead and present them and we will begin with you, Mrs. Burchfield. Welcome. I hope you enjoy your time in Washington before you get back to Tennessee. Please proceed.

TESTIMONY OF FARROLL J. BURCHFIELD, BONNIE EAST, AND RICHARD SHELDON, FORMER PATIENTS OR PATIENT RELATIVES

Mrs. Burchfield. Mr. Chairman, in December of 1966, my son, Ricky Glenn Burchfield, who was then 12 years old, was diagnosed as having chronic myelogenous leukemia. Our family physician told us that he would need to be treated at one of several large hospitals or at a research center and he recommended Oak Ridge Associated University Hospital for several reasons. One, it was close to our home and Rick would be able to be home more. Two, it was a research hospital and at that time—and still today—there had not been a great deal of success in treating myelogenous leukemia. Three, there would be no charges. He told us if we had taken him to Duke or Vanderbilt or some other big hospital, the charges would average around $30,000 a year. The 3 years that he lived would have been around $90,000. We chose to take him to ORAU after the staff there agreed to take him.

His first treatment was cobalt radiation to his spleen. This was very successful. His spleen shrank and he went into a remission that lasted until July 1967. At this time the doctors told us that Rick could either start chemotherapy or even better they would like for him to try "total body radiation." They showed us the room where the treatment would be given and they explained to us that the room had been built with the help of NASA and would be used not only to try to get another remission but the data collected would be used by NASA to study the effects of radiation on man in space.

We chose to try the total body radiation because he had responded so well to the first radiation to the spleen. Rick was in the room 5 days and nights, in complete isolation, but this didn't bother him. He was very good at keeping himself busy and liked to be by himself at times. We could see him through TV screen that monitored him at all times and we could talk to him at any time. It was a very nice room with a color TV and his own telephone. He was told that he could come out at any time if being alone bothered him, but the longer he stayed in the room the quicker the treatment would be over. He chose to stay in the room almost continuously.

The treatment was very comfortable. He had no complaints while he was taking the treatment and he did not even get nauseous as he had with the cobalt to the spleen and he did get a remission from the treatment. While in the room he had electrodes on him that monitored his pulse, respiration, temperature, et cetera. This was for the NASA program to study the effects of radiation on man in space and caused him no discomfort.

After the treatments his doctor told him that they needed to do several bone marrow tests at certain intervals. He asked if this was a part of his treatment or was it for the NASA study. They told him it was for the study so he told them he did not want to have them—they were very painful. The doctor told him that that was all right, they would not do them and would simply write "incomplete" on his testing.

I don't think anyone could have been more honest or open than they were about this. There was also a model of the room there and everyone who worked there told about it and the fact that it was connected to the NASA program.

In September of 1967, Rick was started on myleran, which was the current treatment for his type leukemia and was used mostly to improve the status of the patient and to keep the spleen from enlarging. He took this off and on until early 1969 when his disease turned from chronic to acute and he had to go to large doses of chemotherapy. This was a combination of four drugs, vincristine, 6MP, prednisone and one other drug that I don't remember the name of. The last 10 months were a series of ups and downs with shorter and shorter remissions until he died on December 5, 1969.

I wrote to the National Cancer Institute at Bethesda and gave them my son's diagnosis and asked what the current treatment was, and they wrote back and sent me some literature that showed me that he had gotten at ORAU the same treatment that was being given at Bethesda and all over the United States.

I stayed with my son when he was an inpatient at ORAU at all times except at night. We were both treated very good. The staff, both doctors and nurses, were very professional, yet they had time to do all kinds of things that made Rick comfortable and his hospitalization more enjoyable. I am a medical secretary and I saw nothing from the staff that was not of the highest order. A nurse and an orderly came to our home to go fishing with Rick on one of their off days. He received much more personal care than he would have received in a large hospital.

If he needed someone to play chess or watch a TV program because he could not sleep, there was someone there. The staff knew that he was a sports fan and they always took time to "talk sports" with him. These kind of things were very important to a young teenage boy and helped make his life more normal. He was also allowed to be at home whenever it was possible, and yet when he needed to be in the hospital there was always room for him.

The facilities were not very modern but they were always clean and pleasant. There was a TV room with books, games, et cetera. The nurses and orderlies tried to keep puzzles going, and things like that, to keep the patients interested in doing something.

I have only one regret about the hospital at ORAU. Funds were cut and they could not continue the research. When my son was fighting for his life, a new, very expensive "germ-free room" was built with the hope of using it with the "total body radiation room" to do bone marrow transplants. This was the big hope for myelogenous leukemia at that time. They planned to first put the patient in the total body radiation room to destroy as many leukemic cells as possible and then put the patient in the germ-free environment—so they would not get an infection while their blood count was so low—and then do the bone marrow transplant. President Nixon started cutting funds and my son died asking why. He wanted to try the transplant but there were no funds to try the treatment. This was such a waste, to my way of thinking. The room was built and then no funds to use it.

I knew when I took my son to ORAU that it was a research hospital and I firmly believed that was where he should be in case a cure was found in time to save his life. I am grateful for the treatment my son received at ORAU and I have very warm memories of the staff, the research people, and the other patients there. I am grateful to the U.S. Government for making such a place possible.

Mr. GORE. Thank you, very eloquent testimony. I will withhold questions until others testify.

Mr. GORE. Mrs. East, thank you for being here. We would like to hear from you.

Mrs. EAST. OK. I was referred to ORAU on October 1962 by Dr. Frank Genella, after being diagnosed by Dr. Genella and Dr. Alex Carabia, pathologist at Oak Ridge Hospital, as having idiopathic thrombocytopenic purpura.

I was given steroid therapy at Oak Ridge Hospital, which was the prednisone. I was kept on steroid therapy at the Medical Division and had a splenectomy in November 1962 and continued with the steroid therapy. The steroid therapy was used several other times when needed.

I was fully informed of my treatment at all times. I was always informed of the expected length of treatment. I never received any radiation treatment for my disease. The risk associated with steroid therapy and splenectomy was explained to me. I was never used in any experiment for NASA.

I did sign consent forms upon admission to the Medical Division and prior to the splenectomy.

During my 12 years at the ORAU (ORINS) Medical Division, I had the good fortune to meet many great physicians, and I feel strongly that I had the best treatment available from the entire medical staff. The medical attention I received was excellent. At all times I found the doctors to be extremely compassionate, competent, dedicated, and good moral people.

The care I received from the nurses at the Medical Division was superior.

There was always enough nurses on duty to provide the best of nursing care with love and concern for the patient. The care and concern didn't end with the patient; it extended to the family as well.

Having just weeks before I left the shiny stainless steel and tile environment at the new Oak Ridge Hospital, I was surprised to see what had been the old hospital—now the Medical Division. It had been turned into a bright, cheerful, friendly place with private and semiprivate rooms, furnished very attractively with very up-to-date equipment.

The Medical Division was absolutely immaculate and ample housekeeping staff were employed to maintain the highest degree of cleanliness.

Anything that would add to the patients' care and comfort was provided. That is all.

Mr. **Gore**. Thank you very much.

Richard Sheldon, thank you for being with us.

Mr. **Sheldon**. Thank you. The following are, to the best of my recollection, the events leading up to and including my radiation treatments at Oak Ridge Consolidated Universities.

It was during the summer when I was 15 years old that I was placed in the University of Tennessee Hospital for a common surgery after being diagnosed as having appendicitis. During that surgery, an unexpected development was discovered and later ascertained to be Hodgkin's disease. While I was at U. T. Hospital I was treated, without any success, with chemotherapy, nitrogen mustard, and radiation therapy in the form of X-ray.

My father contacted various doctors in the Knoxville area to find any possible places I might go for more treatment with better results. The only positive feedback he heard was from Dr. Robert Newman, who told my father of the hospital in Oak Ridge where cobalt radiation was being used. Considering the history of Hodgkin's disease, the limited remedy available, the fact that I was virtually dead in a matter of time, we had nothing to lose.

I was admitted to the Oak Ridge facility in the late summer of 1966 and remained a patient at the hospital for approximately 4 months. During this time period I was treated with cobalt radiation to my abdomen and it was explained to me in detail the exact dosage and frequency of treatment. Not seeming relevant at the time, those statistics have long since been forgotten. The only relevant factor at that time was my life, and, with a terminal cancer, a person has absolutely nothing to risk

Outside of my family, the only optimistic outlook I was given was from Dr. Frank V. Comas, who was so sure of my eventual recovery, I never thought of death or even considered myelf a terminal case. Dr. Comas outlined to me and my parents in a comprehensive way what to expect and what not to expect from the treatment. Every test given to me at Oak Ridge was graphically detailed in such a way that a 15-year-old would understand.

The care I received at Oak Ridge can only be described as excellent. The staff was warm, the doctors and nurses were both considerate and comforting. I refuse to believe that these same compassionate people who took care of me were involved in any type of experimental project with humans specifically for the purpose of finding data for NASA.

Since the hospital was a learning institution, I only assumed that any information learned would be handed down to other facilities. I certainly don't see any harm in passing on discoveries to those it may help in the future.

In closing, I must add, I owe that staff my every breath. Need I say more? I salute Oak Ridge Associated Universities. I am very much alive.

Mr. **Gore**. Thank you very much. Thank you. I can tell you really say that with a lot of feeling.

Mrs. Burchfield, your son's illness was first checked by the family physician, was it not?

Mrs. **Burchfield**. Yes.

Mr. GORE. Who was that physician who referred you to——

Mrs. BURCHFIELD. Yes; Dr. Alexander admitted him to Morristown-Hamblem Hospital and did a bone marrow and had it read, and that is where the diagnosis came from. He did not treat him at all. He came and gave us the diagnosis and talked to us about what we could possibly do. And I asked him, since he was also a family friend, "What would you do if it was one of your children?"

He said, "I would get him to Oak Ridge Associated Universities Hospital as fast as possible." Which I did, and in 2 or 3 days he was there.

Mr. GORE. I see. You knew all about the fact it was of an experimental nature?

Mrs. BURCHFIELD. Yes.

Mr. GORE. You said you were told about NASA's involvement?

Mrs. BURCHFIELD. Yes.

Mr. GORE. That didn't trouble you?

Mrs. BURCHFIELD. No; it didn't my son either. He was very proud they could use this information to help the astronauts in space. We knew primarily it was for his benefit, it was a treatment for him, to try to get him in remission, anything, incidentally, didn't bother us.

Mr. GORE. I see. I might say for the record that our three witnesses on this panel are representative of a larger number who contacted the subcommittee to express the point of view that you all have expressed here quite eloquently. There are a large number of such witnesses that we could have called. We chose you all as a representative sample. We appreciate you being here.

Now, your son had the belt attached, the umbilical cord attached?

Mrs. BURCHFIELD. Yes.

Mr. GORE. That was Mrs. Sipes put it on?

Mrs. BURCHFIELD. Yes.

Mr. GORE. Was that the first time you found out about NASA?

Mrs. BURCHFIELD. No; I think from the time I was there, there was the model of the room and everyone knew that it was built—the room was built by NASA and that they were doing this research. I can't remember who originally told me this. I just knew it. Everyone there seemed to know that.

Mr. GORE. Now, did all three of you receive an explanation of possible benefits of alternative treatments, did you feel that the procedures were explained to you enough so you could make a choice, or did you simply rely on their judgment or do you feel like you participated in the decision?

Mrs. EAST. Yes; I did. The first visit as an outpatient I saw Dr. Dave White. And he said to me, "Bonnie, if we cannot help you here, we will send you someplace that can."

Mr. GORE. Can you pull the microphone a little closer?

Mrs. EAST. Did you not hear that?

Mr. GORE. No.

Mrs. EAST. The first visit that I had as an outpatient I saw Dr. Dave White, October 1962. And he said, "Bonnie, if we cannot help you here at ORINS, we will send you someplace that can."

Mr. GORE. Anybody else want to respond to that?

Mr. SHELDON. Let me add that my father is retired from the military and at the time was in the military. So facilities of this Nation were at our disposal. And questioning various doctors in the Knoxville area, he found that the most modern facilities, the most advanced facilities that we would not find any better than those that were at Oak Ridge. OK? And the types of treatment that would help could only be offered at Oak Ridge, compared to various hospitals around that area.

Mr. GORE. And you really feel like you owe your life to that facility, don't you?

Mr. SHELDON. Every breath.

Mr. GORE. All of you signed consent forms?

Mrs. BURCHFIELD. Yes.

Mrs. EAST. Yes.

Mr. SHELDON. Yes.

Mr. GORE. And all of you have extremely positive memories of the people with whom you dealt there?

Mrs. BURCHFIELD. That is right.

Mrs. EAST. Yes.

Mr. SHELDON. Yes.

Mr. GORE. OK.

I would like to note one thing for the record. Earlier I commented on the fact we were not able to obtain all the documents we requested from NASA because these documents were destroyed as part of a routine procedure. I am somewhat troubled that the documents that specifically pertain to this matter had been destroyed. Nevertheless, NASA has spent long hours in a search for the requested documents, and I do appreciate their full cooperation in this matter.

Thank you, our final panel of witnesses, for being here. I wish to thank all of the witnesses who have come long distances and participated in this inquiry. The subcommittee will take this evidence and come to a conclusion based upon it, and we will have a report with conclusions and recommendations within a reasonable period of time. Thank you all very much for participating in a very long day.

The hearing is adjourned.

[Whereupon, at 4:15 p.m., the subcommittee adjourned.]

APPENDIX

ADDITIONAL MATERIAL SUBMITTED FOR THE RECORD

Medium Exposure Rate Total Body Irradiator (METBI)

Construction completed 1959. Facility closed 1974. A concrete shielded room 8' x 8' x 8' containing eight cesium-137 sources. Each source contained approximately 500 curies of ^{137}Cs initially. The facility was usually operated at radiation exposure rates of 1.5 R/min. (90 R/hr.) for therapeutic irradiation although exposure rates of 300 R/hr. down to 1.8 R/hr. were possible. Patients would lay on a bed (constructed of aluminum) located in the center of the room during radiotherapy. Radiation sources were operated remotely and the patient monitored remotely from an instrument console in an adjacent room. Continuous patient surveillance was maintained by closed circuit TV monitors and intercommunication systems.

Low Exposure Rate Total Body Irradiator - (LETBI)

Construction completed 1967. Facility closed 1974. A large concrete shielded room containing an inner treatment room 16' x 16' x 8'. The inter room contained two beds to accommodate two patients to live in for extended period of time (up to 5 days) during radiotherapy. The inner room was designed and furnished like a motel room for the confort of the patients. The outer room contained 10 Cobalt-60 sources geometrically arranged to produce an isodose level of 1.5 R/hr. anywhere within the inner treatment room. Initially each source contained approximately 26 curies of ^{60}Co. The sources were operated and monitored remotely from an instrument console located in an adjacent room. Closed circuit TV monitors and intercommunication systems were utilized for continuous surveillance of patients. In addition, a physiologic monitoring system was employed for continuous monitoring of each patients physiological functions through out the treatment period.

LOW-EXPOSURE TOTAL BODY IRRADIATOR-PROTRACTED RX

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
511693	WP	61	IT Thrombo- cythemia	^{60}Co Lctbi	6-12-67	1.5r/hr	150r
411504	GL	76	CLL	"	7-17-67		100r
611806	EB	12	CGL	"	7-31-67		100r
611731	RS	46	CGL		8-21-67		100r
X 611747	WR	79	Lymphoma		8-28-67		100r
611741	MF	55	CGL		11-6-67		100r
611716	OD	61	PJ		12-11-67		100r
411504	CC	77	CLL		12-11-67		100r
811906	EB	62	LS		4-8-68		250r
611782	CC	83	CGL		4-29-68		100r
811915	AS	66	CGL		4-29-68		100r
611716	OD	61	PV		5-7-68		250r
511693	WP	62	IT		5-13-68		150r
011139	ES	59	PV		6-17-68		230r
511676	CM	74	PV		7-15 68		250r
811950	BJ	59	LS		9-30-68		250r
911998	FC	55	LS		3-24-69		250r
912000	FM	63	LS		4-7-69		250r
911050	FW	77	PV		4-21-69		250r
912058	EF	52	CGL		9-1-69		250r
912068	LH	61	IT		9-29-69		150r
912077	ES	28	CGL		10-27-69		150r
912094	JK	65	CGL		11-9-69		Discont.
912055	ES	69	LS		12-15-69		100r
912107	WM	59	PRV		12-29-69		150r
811947	WA	42	CGL		1-12-70		250r
912093	MG	69	CGL		1-19-70		150r
511676	CM	76	PRV		2-5-70		150r
611731	RS	48	CGL		3-9-70		150r
012120	MD	69	CLL		3-23-70		100r
X 012151	WP	45	Lymphoma		4-6-70		100r
912058	BF	52	CGL		4-20-70		150r
811892	CC	61	CLL		6-9-70		100r
611731	RS	48	CGL		8-10-70		150r

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
912058	BF	53	CGL	^{60}Co LETBI	8-17-70	1.5r/hr	150r
012228	KW	52	CGL		9-28-70		250r
511693	WP	64	IT		10-26-70		150r
811893	CC	61	CLL		11-8-70		100r
912107	WM	60	PRV		12-7-70		150r
912055	BS	70	LS		12-70		140r
611731	RS	49	CGL		1-17-71		150r
912044	LB	37	CGL		2-15-71		150r
912110	LH	57	PRV		3-22-71		150r
112311	AO	73	PRV		4-12-71		150r
611731	RS	49	CGL		4-26-71		200r
912044	LB	38	CGL		5-3-71		200r
111283	JW	66	PRV		6-1-71		100r
912110	EH	58	PRV		8-16-71		100r
611716	OP	64	PRV		8-30-71		150r
912094	JK	67	CGL		10-11-71		150r
912055	BS	71	LS		10-25-71		150r
112369	JO	50	LS		11-8-71		101.5r
912068	LH	63	IT		11-30-71		150r
611716	OD	64	PRV		1-3-72		150r
112383	LM	61	CGL		1-3-72		100r
511693	WP	66	IT		1-10-72		150r
912110	EH	59	PRV		2-14-72		100r
111283	JW	66	PRV		2-14-72		100r
112369	JO	50	LS		3-27-72		30r
211401	WW	54	PRV		4-10-72		150r
511693	WP	66	IT		4-24-72		100r
811918	IT	54	CGL		5-8-72		250r
212499	MB	49	CGL		10-2-72		250r
212551	MT	47	CGL		10-9-72		250r
611716	CD	66	PRV		10-23-72		150r
112394	EW	63	CGL		12-4-72		222.1r
912094	JK	69	CGL		1-29-73		150r
312632	JN	44	CGL		5-14-73		250r
312637	FP	62	Lymphoma		6-13-73		10r
312648	LA	66	CGL		7-15-73		150r
312662	FS	72	CLL		8-13-73		100r

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
312662	RS	72	CLL	^{60}Co LETBI	10-8-73	1.5r/hr	100r
912110	EH	63	PRV		10-22-73		100r
012205	EM	50	CLL		11-5-73		100r
212555	JS	55	PRV		2-6-74		150r
412718	JM	44	Lymphoma		2-25-74		100r
312640	CF	76	CLL		3-8-74		100r

METBI CASES

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
210159	HC	55	Polychthemia vera	^{137}Cs METBI	5-4-65	100r	
610616	FS	67	CLL	^{60}Co Red Menace	9-29-59	50r	
610616	FS	67	CLL	^{137}Cs METBI	4-21-64	50r	
610662	JS	58	Acute myeloid leukemia	^{137}Cs METBI	3-13-62	300r	
710756	BG	63	CLL	^{137}Cs METBI	6-7-60	50r	
710779	WH	66	Subacute myeloid leukemia	^{60}Co Westinghouse	6-9-59 6-19-59	10Rx5	90r
710800	TM	63	Polycythemia Vera	^{137}Cs METBI	2-23-65	100r	
710806	BMA	77	Lymphosarcoma	^{137}Cs METBI	10-3-61	100r	
710813	LP	14	Acute leukemia		8-14-58	50r	
810843	DC	8	CLL	^{60}Co Red Menace	10-29-58	301r	
810858	GW	55	CLL	^{137}Cs METBI	6-28-60	50r	
810863	AW	17	Acute leukemia	^{60}Co Red Menace	10-1-58	395r	
810923	FH		Polycythemia Vera	^{137}Cs METBI	5-18-65	100r	
810936	LH	8	Acute leukemia	^{60}Co Red Menace	10-22-58	490r	
910965	MS	17	Prostatic Rhabomyosarcoma	^{60}Co Red Menace	3-3-59	400r	
910989	SW	2	ALL	^{60}Co Red Menace	4-16-59	360r	
911017	DMcK	4	Acute Leukemia	^{60}Co Westinghouse	6-15-59 6-23-59	20Rx7	140r
911017	DmcK	4	" "	"	6-24-59 6-25-59	400Rx2	800r
911046	BR	51	CLL	^{60}Co Red Menace	9-29-59	50r	
911046	BR	54	CLL	^{137}Cs METBI	6-19-62	50r	
911050	MW	73	Polycythemia Vera	^{137}Cs METBI	2-9-65	100r	
911050	MW	75	" "	"	1-17-67	100r	
911073	SK	25	Lymphosarcoma	^{60}Co Westinghouse	1-25-59	50r	
011079	HM	70	CLL	^{60}Co Westinghouse	1-12-60	50r	
011082	MY	31	Sympathicogonioma	^{60}Co Red Menace	2-2-60	360r	
011084	BP	21	Hodgkin's	^{60}Co Westinghouse	2-16-60	50r	
011088	JG	51	CLL	^{60}Co Westinghouse	4-5-60	50r	
011088	JG	54	CLL	^{137}Co METBI	4-3-62	100r	
011088	JG	55	CLL	^{137}Co METBI	8-27-63	100r	
011110	DC	49	Lymphosarcoma	^{137}Cs METBI	5-3-60	100r	
011110	DC	51	"	"	2-20-62	100r	
011118	VH	67	Chronic Myeloid leukemia	^{137}Cs METBI	5-3-60	50r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
011125	MW	70	CLL	^{137}Cs METBI	6-28-60	50r	
011136	BW	51	Ca. Breast w/ Metastases	"	6-28-60	100r	
011156	ES	48	Lymphosarcoma	^{137}Cs METBI	7-26-60	100r	
011167	RP	47	Chronic Myeloid leukemia	"	8-16-60	50r	
011175	RG	39	Lymphosarcoma	^{137}Cs METBI	9-13-60	100r	
011183	LT	52	Chronic Myeloid Leukemia	^{137}Cs METBI	9-20-60	50r	
011183	LT	56	Chronic Myeloid Leukemia	"	1-12-65	50r	
011192	SH	8	Acute Leukemia	"	5-2-61	300r	
011192	SH	8	"	"	6-20-61	50r	
011192	SH	8	"	"	7-6-61	50r	
011192	SH	8	"	"	7-18-61	50r	
011192	SH	8	"	"	8-1-61	50r	
011192	SH	8	"	"	8-22-61	25r	
011203	JQ	58	CLL	^{137}Cs METBI	10-25-60	50r	
011203	JQ	62	CLL	^{137}Cs METBI	3-10-64	50r	
011209	JH	12	Hodgkin's	"	11-15-60	300r	
011220	AW	65	"	"	12-6-60	100r	
011224	TF	5	Acute Leukemia	"	3-6-62	300r	
011227	HP	40	"	"	12-13-60	100r	
011229	RB	3	"	"	2-13-62	300r	
111235	AA	43	Subacute Myeloid Leukemia	"	5-9-61	100r	
111237	DH	16	Lymphosarcoma	^{137}Cs METBI	7-25-61	300r	
111242	BCS	32	"	"	1-31-61	50r	
111242	BCS	32	"	"	5-2-61	100r	
111241	BCS	33	"	"	5-29-62	100r	
111248	LH	46	"	"	8-14-62	50r	
111251	JM	74	CLL	"	8-8-61	50r	
111264	WL	42	Lymphosarcoma	"	5-22-62	50r	
111264	WL	45	"	"	6-29-65	100r	
111266	WL	82	Mycosis Fungoides	"	7-7-61	100r	
111274	JR	20	Hodgkin's	"	6-6-61	100r	
111278	RC	47	Lymphosarcoma	"	6-19-62	100r	
111304	CR	49	CLL	"	9-19-61	100r	

#	Initial	Age	Diagnosis	Source	Date	TDI	Total Dose
111305	FB	3	X Acute Leukemia	^{137}Cs METBI	1-30-62	300r	
211337	EP	60	Chronic Myeloid leukemia	"	3-6-62	50r	
211337	EP	62	"	"	3-16-65	50r	
211337	EP	63	"	"	2-22-66	100r	
211344	MJ	81	CLL	"	3-13-62	50r	
211345	LH	35	Acute Leukemia	"	2-19-63	300r	
211349	JS	70	Lymphosarcoma	"	4-10-62	100r	
211351	TW	50	"	"	3-27-62	100r	
211355	BT	63	Chronic Myeloid leukemia	"	5-8-62	50r	
211360	TA	10	Rhabdomysarcoma	"	7-31-62	200r	
211375	WB	50	Chronic Myeloid leukemia	"	2-21-67	100r	
211383	RL	59	Lymphosarcoma	"	7-17-62	100r	
211383	RL	59	"	"	7-16-63	100r	
211389	HB	69	Acute Leukemia	"	10-9-62	100r	
211390-	WN	76	Lymphosarcoma	"	7-31-62	100r	
211390	WN	78	"	"	2-11-64	100r	
211411	DB	10	Acute Leukemia	"	12-31-63	300r	
311346	CC	49	Lymphosarcoma	"	2-12-63	100r	
311430	HA	11	Acute Leukemia	"	1-10-63	300r	
311434	CK	87	Lymphosarcoma	"	2-26-63	100r	
311437	RK	17	Acute Leukemia	"	2-5-63	300r	
311457	CW	58	CLL	"	4-7-64	50r	
311465	GH	55	Lymphosarcoma	"	4-30-63	100r	
311465	GH	57	"	"	9-29-64	100r	
311479	LB	63	CLL	"	7-2-63	50r	
311480	MW	50	Acute Myelomonocytic leukemia	"	6-25-63	100r	
311496	JA	6	Acute Leukemia	"	8-27-63	100r	
311517	EW	55	Lymphosarcoma	"	10-29-63	100r	
311518	RC	9	Acute Leukemia	"	8-11-64	100r	
411529	SC	7	"	"	1-21-64	300r	
411532	JS	88	CLL	"	1-28-64	100r	
411538	CC	8	CLL	"	8-17-65	300r	
411542	EJ	88	CLL	"	2-25-64	100r	
411543	WMcK	72	Giant Follicular lymphosarcoma	"	2-18-64	50r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
411545	HC	61	Lymphosarcoma	^{137}Cs METBI	3-30-65	100r	
411546	MC	63	"	"	3-1-66	100r	
411549	EB	57	CLL	"	3-10-64	100r	
411553	JS	54	CLL	"	3-31-64	100r	
411562	BW	65	Lymphosarcoma	"	5-5-64	100r	
411573	BN	42	Multiple Myeloma	"	6-1-65	200r	
411574	DY	7	Acute Leukemia	"	6-16-64	300r	
411577	NT	69	Polycythemia Vera	"	7-7-64	100r	
411578	LC	61	CLL	"	7-7-64	100r	
411578	LC	62	CLL	"	4-26-66	100r	
411591	MB	71	CLL	"	8-11-64	100r	
411596	OS	72	Lymphosarcoma	"	8-25-64	100r	
411604	GC	74	CLL	"	9-22-64	100r	
411604	GC	75	CLL	"	3-22-66	100r	
411618	TO	69	CLL	"	11-24-64	100r	
411625	IR	48	Subacute Monomyelocytic Leukemia	"	1-5-65	100r	
511635	MS	76	CLL	"	3-23-65	100r	
511637	JA	71	CLL	"	3-30-65	100r	
511669	EL	54	Chronic Myeloid Leukemia	"	11-29-66	100r	
511670	DS	6	Acute Leukemia	"	12-3-68	353r	
511671	HG	78	Lymphosarcoma	"	8-24-65	100r	
511693	WP	60	Primary Thrombocythemia	"	3-8-66	100r	
511693	WP	63	"	"	4-21-69	30Rx5	150r
511693	WP	66	"	"	6-29-72	30r	
511693	WP	66	"	"	9-21-72	30r	
511693	WP	66	"	"	11-16-72	30r	
511693	WP	67	"	"	1-16-73	30r	
511693	WP	67	"	"	7-3-73	30r	
511693	WP	"	"	"	7-10-73	30r	
511693	WP	"	"	"	8-23-73	30r	
511693	WP	"	"	"	9-6-73	30r	
511693	WP	"	"	"	9-20-73	30r	
511693	WP	"	"	"	10-4-73	30r	
511693	WP	"	"	"	10-18-73	30r	
511693	WP	"	"	"	11-1-73	30r	
511693	WP	68	"	"	12-27-73	30r	
511693	WP	"	"	"	1-24-74	30r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
511693	WP	68	Primary Thrombocythemia	^{137}Cs METBI	2-21-74	30r	
511693	WP	"	"	"	3-21-74	30r	
511693	WP	"	"	"	5-30-74	30r	
511693	WP	"	"	"	7-25-74	30r	
511705	LF	55	CLL	"	11-30-65	100r	
611716	OD	59	Polycythemia Vera	"	1-25-66	100r	
611716	OD	64	"	"	12-7-70	30Rx5	150r
611721	CF	41	Lymphosarcoma	"	2-1-66	100r	
611724	AM	67	"	"	3-22-66	100r	
611731	SS	45	Chronic Myeloid Leukemia	"	11-21-67	100r	
611731	SS	46	"	"	5-2-68	25Rx4	100r
611731	SS	48	"	"	9-19-69	30Rx5	150r
611747	WR	78	Lymphosarcoma	"	5-24-66	100r	
611796	CB	44	"	"	11-29-66	50r	
711847	DR	62	Reticulum Cell sarcoma	"	7-25-67	141r	
811915	AS	69	CGL	"	2-22-71	30Rx5	150r
811918	JT	54	CGL	"	12-6-72	30r	
811918	"	"	"	"	1-3-73	30r	
811918	"	"	"	"	1-16-73	30r	
811918	"	"	"	"	1-31-73	30r	
811918	"	"	"	"	2-7-73	30r	
811918	"	"	"	"	2-14-73	30r	
811918	"	55	"	"	3-1-73	30r	
811918	"	"	"	"	3-7-73	30r	
811918	"	"	"	"	3-28-73	30r	
811918	"	"	"	"	4-11-73	30r	
811918	"	"	"	"	4-25-73	30r	
811918	"	"	"	"	5-16-73	30r	
811918	"	"	"	"	6-13-73	30r	
811918	"	"	"	"	7-5-73	30r	
811918	"	"	"	"	7-26-73	30r	
811918	"	"	"	"	8-15-73	30r	
811918	"	"	"	"	9-5-73	30r	
811918	"	"	"	"	9-26-73	30r	
811918	"	"	"	"	10-17-73	30r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
811918	JT	55	CGL	^{137}Cs METBI	11-7-73	30r	
811918	"	"	"	"	12-6-73	30r	
811918	"	"	"	"	12-26-73	30r	
811918	"	"	"	"	1-17-74	30r	
811918	"	"	"	"	1-31-74	30r	
811918	"	"	"	"	2-15-74	30r	
811918	"	56	"	"	3-14-74	30r	
811918	"	"	"	"	4-3-74	30r	
811918	"	"	"	"	4-17-74	30r	
811918	"	"	"	"	5-1-74	30r	
811918	"	"	"	"	5-15-74	30r	
811918	"	"	"	"	5-30-74	30r	
811918	"	"	"	"	6-17-74	30Rx5	150r
811918	"	"	"	"	8-8-74	30r	
811918	"	"	"	"	8-20-74	30r	
811918	"	"	"	"	9-5-74	30r	
811918	"	"	"	"	9-19-74	30r	
811947	WA	43	CCL	"	1-25-71	30Rx5	150r
811947	WA	"	"	"	9-20-71	30Rx5	150r
811950	RJ	60	Lymphosarcoma	"	3-24-69	31.25Rx8	250r
911984	JE	69	CLL	"	6-19-73	10r	
911984	JE	"	"	"	7-9-73	10r	
911984	JE	"	"	"	7-11-73	10r	
911984	JE	"	"	"	7-13-73	10r	
911984	JE	"	"	"	8-13-73	10r	
911994	MS	55	CGL	"	5-10-71	30Rx5	150r
912007	IB	60	Lymphosarcoma	"	6-9-69	30Rx5	150r
912044	LB	38	CGL	"	8-24-71	30Rx4	120r
912044	LB	"	"	"	9-21-71	30r	
912044	LB	"	"	"	11-9-71	30r	
912044	LB	"	"	"	11-16-71	30r	
912044	LB	"	"	"	12-14-71	30r	
912044	LB	"	"	"	1-4-72	30r	
912044	LB	"	"	"	2-2-72	30r	
912044	LB	"	"	"	2-29-72	30r	
912044	LB	"	"	"	3-14-72	30r	
912044	LB	"	"	"	3-28-72	30r	
912044	LB	"	"	"	4-11-72	30r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
912044	LB	38	CGL	^{137}Cs METBI	4-25-72	30r	
912044	LB	"	"	"	5-9-72	30r	
912044	LB	39	"	"	1-16-73	30r	
912044	LB	"	"	"	2-7-73	30r	
912044	LB	"	"	"	3-6-73	30r	
912044	LB	"	"	"	3-20-73	30r	
912044	LB	"	"	"	4-3-73	30r	
912044	LB	40	"	"	4-17-73	30r	
912044	LB	"	"	"	5-2-73	30r	
912044	LB	"	"	"	5-15-73	30r	
912044	LB	"	"	"	6-7-73	28r	
912044	LB	"	"	"	6-20-73	30r	
912044	LB	"	"	"	7-11-73	30r	
912044	LB	"	"	"	7-24-73	30r	
912044	LB	"	"	"	8-21-73	30r	
912044	LB	"	"	"	9-4-73	30r	
912044	LB	"	"	"	9-18-73	30r	
912044	LB	"	"	"	9-25-73	30r	
912044	LB	"	"	"	10-2-73	30r	
912044	LB	"	"	"	10-9-73	30r	
912044	LB	"	"	"	10-23-73	30r	
912055	BS	71	Lymphosarcoma	^{137}Cs METBI	5-25-72	30r	
912055	BS	"	"	"	7-3-72	10Rx3 M,W,F	30r
912055	BS	"	"	"	7-10-72	10Rx3	30r
912055	BS	"	"	"	7-17-72	10Rx3	30r
912055	BS	"	"	"	7-24-72	10Rx3	30r
912055	BS	"	"	"	7-31-72	10Rx3	30r
912055	BS	72	"	"	12-4-72	10Rx3	30r
912055	BS	"	"	"	12-11-72	10Rx3	30r
912055	BS	"	"	"	12-18-72	10Rx3	30r
912055	BS	"	"	"	2-1-73	10r	
912055	BS	"	"	"	2-5-73	10Rx3	30r
912055	BS	"	"	"	2-12-73	10Rx3	30r
912055	BS	"	"	"	2-19-73	10Rx2	20r
912055	BS	73	"	"	7-10-73	30r	
912055	BS	"	"	"	7-24-73	30r	
912055	BS	"	"	"	10-2-73	30r	
912055	BS	"	"	"	11-6-73	30r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
912055	BS	73	Lymphosarcoma	^{137}Cs METBI	11-20-73	30r	
912055	BS	73	"	"	12-18-73	30r	
912055	BS	73	"	"	1-8-74	30r	
912055	BS	73	"	"	1-29-74	30r	
912055	BS	73	"	"	2-26-74	30r	
912055	BS	73	"	"	4-23-74	30r	
912055	BS	73	"	"	7-16-74	30r	
912068	LH	66	Idiopathic Thrombocythemia	"	5-30-74	30r	
912068	LH	"	"	"	9-12-74	30r	
912093	MJ	68	CGL	"	11-10-69	30Rx5	150r
912093	MJ	70	"	"	6-26-72	30Rx5	150r
912093	MJ	"	"	"	3-12-73	30Rx5	150r
912093	MJ	73	"	"	2-4-74	30Rx5	150r
912093	MJ	"	"	"	8-12-74	30Rx5	150r
912094	JK	68	"	"	1-27-72	30r	
912094	JK	"	"	"	4-20-72	30r	
912094	JK	"	"	"	7-20-72	30r	
912094	JK	"	"	"	10-19-72	30r	
912094	JK	69	"	"	5-3-73	30r	
912094	JK	"	"	"	5-10-73	30r	
912094	JK	"	"	"	5-17-73	30r	
912094	JK	"	"	"	8-9-73	30r	
912094	JK	"	"	"	9-13-73	30r	
912094	JK	"	"	"	10-11-73	30r	
912094	JK	"	"	"	12-13-73	30r	
912094	JK	"	"	"	1-2-74	30r	
912094	JK	"	"	"	1-31-74	30r	
912110	EH	59	Polycythemia Vera	"	7-21-72	10r	
912110	EH	"	"	"	7-28-72	10r	
912110	EH	"	"	"	9-1-72	10r	
912110	EH	"	"	"	9-8-72	10r	
912110	EH	"	"	"	9-15-72	10r	
912110	EH	59	"	"	9-22-72	10r	
912110	EH	"	"	"	10-13-72	10r	
912110	EH	"	"	"	10-27-72	10r	
012146	CW	68	Lymphosarcoma	"	8-16-71	10Rx10	100r
012146	CW	"	"	"	9-20-71	10Rx5	50r

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
012205	EM	50	CLL	^{137}Cs METBI	1-22-74	10r	
012205	EM	50	CLL	"	2-12-74	10r	
012205	EM	50	CLL	"	2-26-74	30r	
012205	EM	50	CLL	"	6-18-74	30r	
012228	CW	53	CGL	"	4-5-71	30Rx5	150r
012228	CW	53	CGL	"	9-7-71	30Rx8	240r
112288	EL	67	CGL	"	10-23-72	10Rx3	30r
112288	EL	"	"	"	10-30-72	10Rx3	30r
112288	EL	"	"	"	11-6-72	10Rx3	30r
112288	EL	"	"	"	11-13-72	10Rx3	30r
112311	AO	74	Polycythemia Vera	"	2-28-72	30Rx5	150r
112312	GW	79	Polycythemia Vera	"	5-7-71	30Rx5	150r
112394	BW	62	CCL	"	1-15-71	30Rx5	150r
112394	BW	"	"	"	12-23-71	30r	
112394	BW	"	"	"	1-27-72	30r	
112394	BW	"	"	"	2-10-72	30r	
112394	BW	"	"	"	2-24-72	30r	
112394	BW	"	"	"	3-9-72	30r	
112394	BW	"	"	"	3-23-72	30r	
112394	BW	"	"	"	4-20-72	30r	
112401	RB	"	"	"	1-4-73	10r	
112417	GG	68	CLL	^{137}Cs METBI	10-24-72	10r	
112417	GG	"	"	"	10-31-72	10r	
112417	GG	"	"	"	11-7-72	10r	
112417	GG	"	"	"	11-14-72	10r	
112417	GG	"	"	"	11-21-72	10r	
112417	GG	"	"	"	11-28-72	10r	
112417	GG	"	"	"	1-2-73	10r	
112417	GG	"	"	"	1-16-73	10r	
112417	GG	"	"	"	2-16-73	10r	
112417	GG	"	"	"	3-2-73	10r	
112417	GG	"	"	"	5-29-73	10r	
112417	GG	"	"	"	6-26-73	10r	
112417	GG	"	"	"	7-24-73	10r	
112417	GG	69	"	"	8-21-73	10r	
112417	GG	"	"	"	9-12-73	10r	
112417	GG	"	"	"	10-2-73	10r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
112417	GG	69	CLL	^{137}Cs METBI	10-23-73	10r	
112417	"	"	"	"	12-6-73	10r	
112417	"	"	"	"	1-8-74	10r	
112417	"	"	"	"	1-29-74	10r	
112417	"	"	"	"	2-19-74	10r	
112417	"	"	"	"	3-20-74	10r	
112417	"	"	"	"	4-16-74	10r	
112417	"	"	"	"	5-15-74	10r	
212462	SK	72	CCL	^{137}Cs METBI	3-17-72	30Rx5	150r
212462	"	"	"	"	3-22-72	30Rx3	90r
212462	"	"	"	"	5-5-72	30r	
212462	"	"	"	"	5-12-72	30r	
212462	"	"	"	"	5-19-72	30r	
212462	"	"	"	"	7-18-72	30r	
212462	"	"	"	"	7-25-72	30r	
212462	"	"	"	"	8 1-72	30r	
212462	"	"	"	"	8-8-72	30r	
212462	"	"	"	"	9-19-72	30r	
212462	"	"	"	"	10-4-72	30r	
212462	"	"	"	"	10-12-72	30r	
212462	"	"	"	"	10-20-72	30r	
212462	"	"	"	"	10-31-72	30r	
212462	"	73	"	"	12-7-72	30r	
212462	"	"	"	"	12-22-72	30r	
212462	"	"	"	"	1-2-73	30r	
212462	"	"	"	"	1-10-73	30r	
212462	"	"	"	"	1-16-73	30r	
212462	"	"	"	"	2-22-73	30r	
212462	"	"	"	"	3-5-73	30r	
212462	"	"	"	"	3-12-73	30r	
212462	"	"	"	"	3-16-73	30r	
212462	"	"	"	"	3-21-73	30r	
212462	"	"	"	"	3-22-73	30r	
212462	"	"	"	"	3-23-73	30r	
212462	"	"	"	"	4-2-73	30r	
212462	"	"	"	"	4-30-73	30r	
212462	"	"	"	"	5-7-73	30r	
212462	"	"	"	"	5-14-73	30r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
212462	SM	73	CGL	^{137}Cs METBI	5-21-73	30r	
212462	SM	"	"	"	5-30-73	30r	
212462	SM	"	"	"	6-4-73	30r	
212462	SM	"	"	"	7-9-73	30r	
212462	SM	"	"	"	7-16-73	30r	
212462	SM	"	"	"	7-23-73	30r	
212462	SM	"	"	"	7-30-73	30r	
212462	SM	"	"	"	8-6-73	30r	
212462	SM	"	"	"	8-13-73	30r	
212462	SM	"	"	"	8-20-73	30r	
212462	SM	"	"	"	9-10-73	30r	
212462	SM	"	"	"	9-17-73	30r	
212462	SM	"	"	"	9-24-73	30r	
212462	SM	"	"	"	9-28-73	30r	
212462	SM	"	"	"	10-8-73	30r	
212462	SM	"	"	"	10-15-73	30r	
212462	SM	"	"	"	10-22-73	30r	
212462	SM	"	"	"	10-29-73	30r	
212462	SM	"	"	"	11-5-73	30r	
212462	SM	"	"	"	11-9-73	30r	
212462	SM	"	"	"	11-13-73	30r	
212462	SM	"	"	"	11-21-73	30r	
212462	SM	"	"	"	11-28-73	30r	
212462	SM	74	"	"	12-5-73	30r	
212462	SM	"	"	"	12-14-73	30r	
212462	SM	"	"	"	12-19-73	30r	
212462	SM	"	"	"	12-26-73	30r	
212462	SM	"	"	"	1-2-74	30r	
212462	SM	"	"	"	1-9-74	30r	
212462	SM	"	"	"	1-16-74	30r	
212462	SM	"	"	"	1-30-74	30r	
212462	SM	"	"	"	2-4-74	30r	
212462	SM	"	"	"	2-8-74	30r	
212462	SM	"	"	"	2-11-74	30r	
212462	SM	"	"	"	2-15-74	30r	
212462	SM	"	"	"	2-18-74	30r	
212462	SM	"	"	"	2-22-74	30r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
212462	SM	74	CGL	^{137}Cs METBI	2-25-74	30r	
212462	SM	"	"	"	3-1-74	30r	
212462	SM	"	"	"	3-13-74	30r	
212462	SM	"	"	"	3-18-74	30r	
212462	SM	"	"	"	4-12-74	30r	
212483	PC	59	CLL	"	7-10-72	10Rx3 M,W,F	30r
212483	"	"	"	"	7-17-72	10Rx3	30r
212483	"	"	"	"	7-24-72	10Rx3	30r
212483	"	"	"	"	7-31-72	10Rx3	30r
212483	"	"	"	"	8-7-72	10Rx3	30r
212505	SF	71	CGL	"	11-7-72	30r	
212505	SF	"	"	"	12-6-72	30r	
212505	SF	"	"	"	12-26-72	30r	
212505	SF	"	"	"	1-23-73	30r	
212505	SF	72	"	"	5-15-73	30r	
212505	SF	"	"	"	6-12-73	30r	
212505	SF	"	"	"	7-3-73	30r	
212505	"	"	"	"	7-31-73	30r	
212505	"	"	"	"	2-26-74	30r	
212505	"	73	"	"	6-10-74	30r	
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212515	"	"	"	"	3-19-74	30r	
212515	"	"	"	"	4-11-74	30r	
212515	"	"	"	"	4-16-74	30r	
212515	"	"	"	"	4-23-74	30r	
212515	"	"	"	"	5-14-74	30r	
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212515	"	"	"	"	5-30-74	30r	
212515	"	49	"	"	9-10-74	30r	
212620	BC	41	CLL	^{137}Cs METBI	4-4-73	30Rx5	150r

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
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312632	JN	44	CGL	"	7-27-73	30r	
312632	"	"	"	"	8-6-73	30r	
312632	"	"	"	"	8-9-73	30r	
312632	"	"	"	"	8-13-73	30r	
312632	"	"	"	"	8-16-73	30r	
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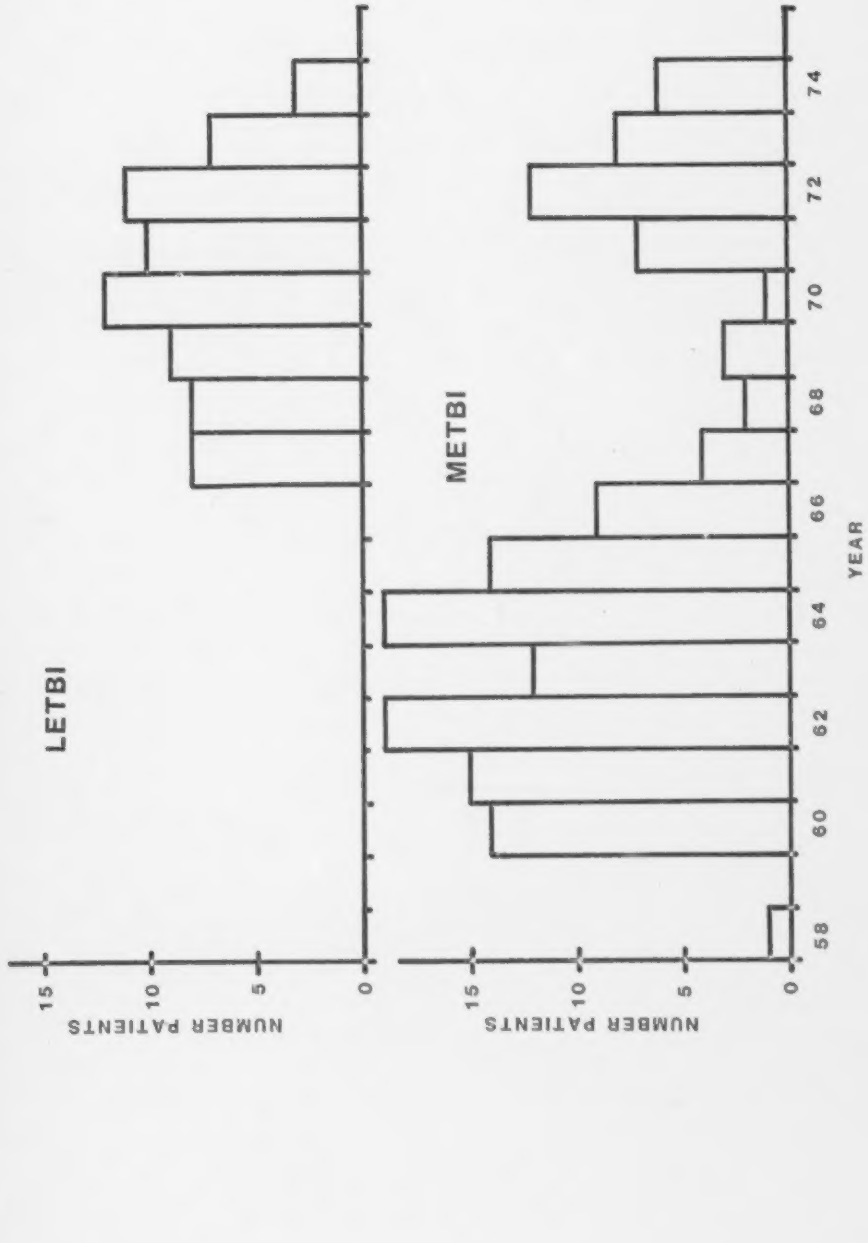
312632	"	"	"	"	7-25-74	30r	
312632	"	"	"	"	8-1-74	30r	
312632	"	"	"	"	8-8-74	30r	
312632	"	"	"	"	8-15-74	30r	
312632	"	"	"	"	8-22-74	30r	
312632	"	"	"	"	8-29-74	30r	
312632	"	"	"	"	9-12-74	30r	
312633	DD	51	Polycythemia Vera	"	7-8-74	30Rx5	150r
312640	CF	76	CLL	"	2-25-74	10Rx5	50r
312640	"	"	"	"	7-23-74	30r	
312648	LA	66	CGL	"	9-6-73	10r	
312648	"	"	"	"	9-13-73	30r	

#	Initial	Age	Diagnosis	Source	Date	TBI	Total Dose
312648	LA	66	CGL	^{137}Cs METBI	11-8-73	30r	
312648	LA	"	"	"	12-7-73	30r	
312648	LA	"	"	"	12-21-73	30r	
312648	"	"	"	"	1-18-74	30r	
312648	"	"	"	"	2-22-74	30r	
312648	"	"	"	"	4-12-74	30r	
312672	MR	81	CLL	"	8-17-73	10r	
312672	"	"	"	"	9-7-73	10r	
312672	"	"	"	"	10-2-73	10r	
312672	"	"	"	"	10-30-73	10r	
312672	"	"	"	"	12-7-73	10r	
312672	"	"	"	"	1-18-74	10r	
312672	"	"	"	"	3-1-74	10r	
312698	SK	55	Polycythemia Vera	"	10-29-73	30Rx5	150r
412776	EW	66	Polycythemia Vera	"	8-19-74	30Rx5	150r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METBI
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NUMBER PATIENTS
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64
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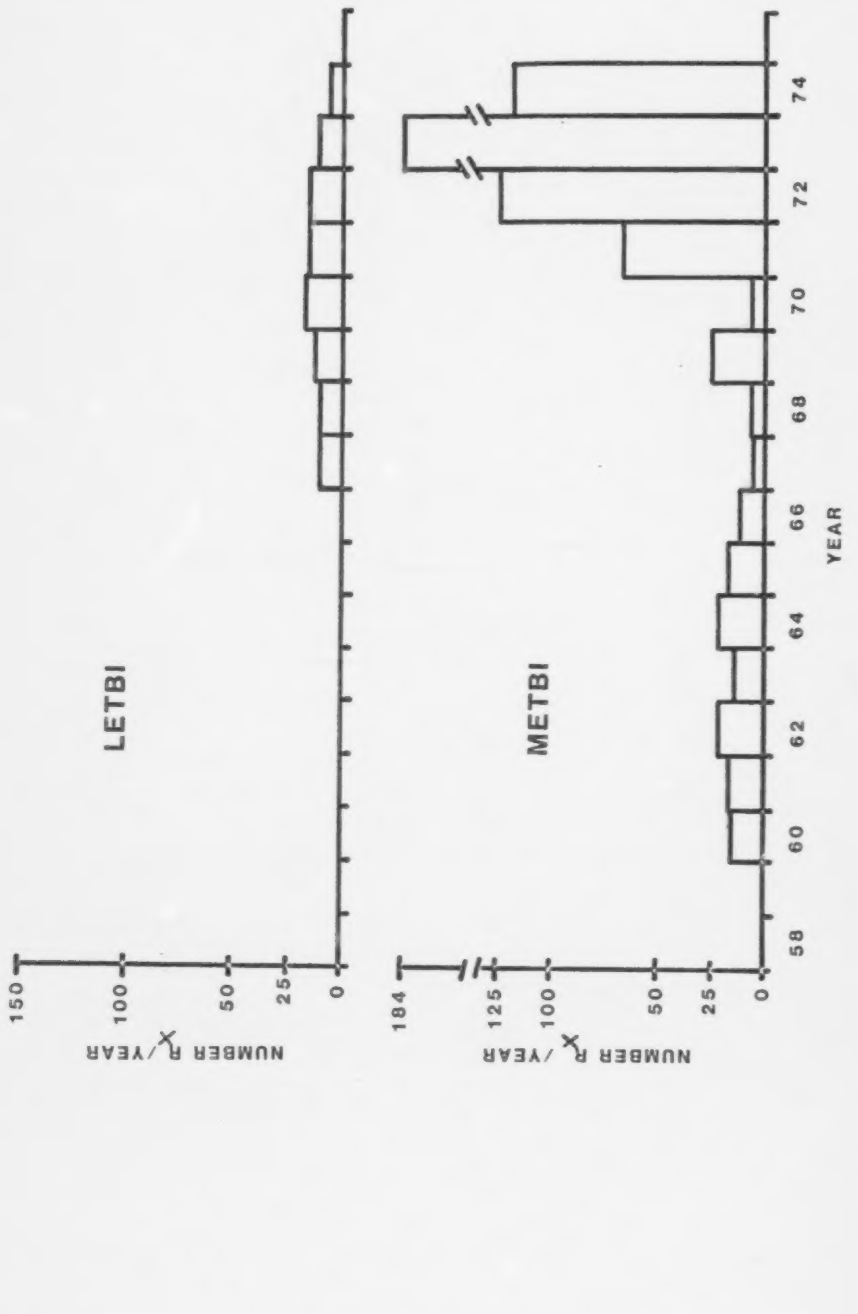
YEAR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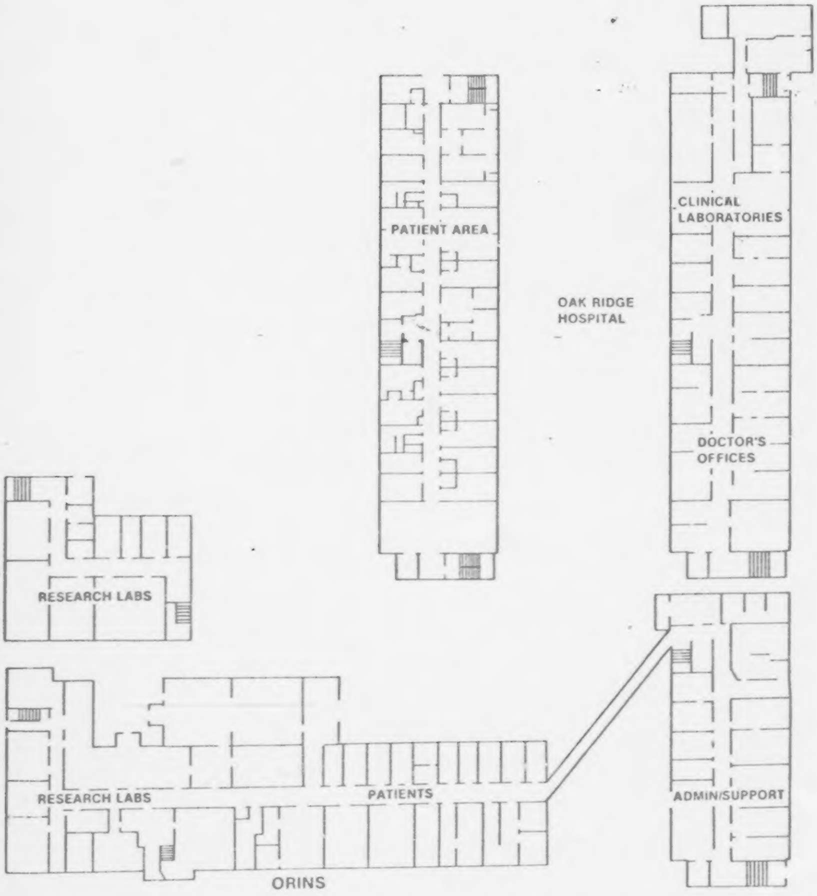
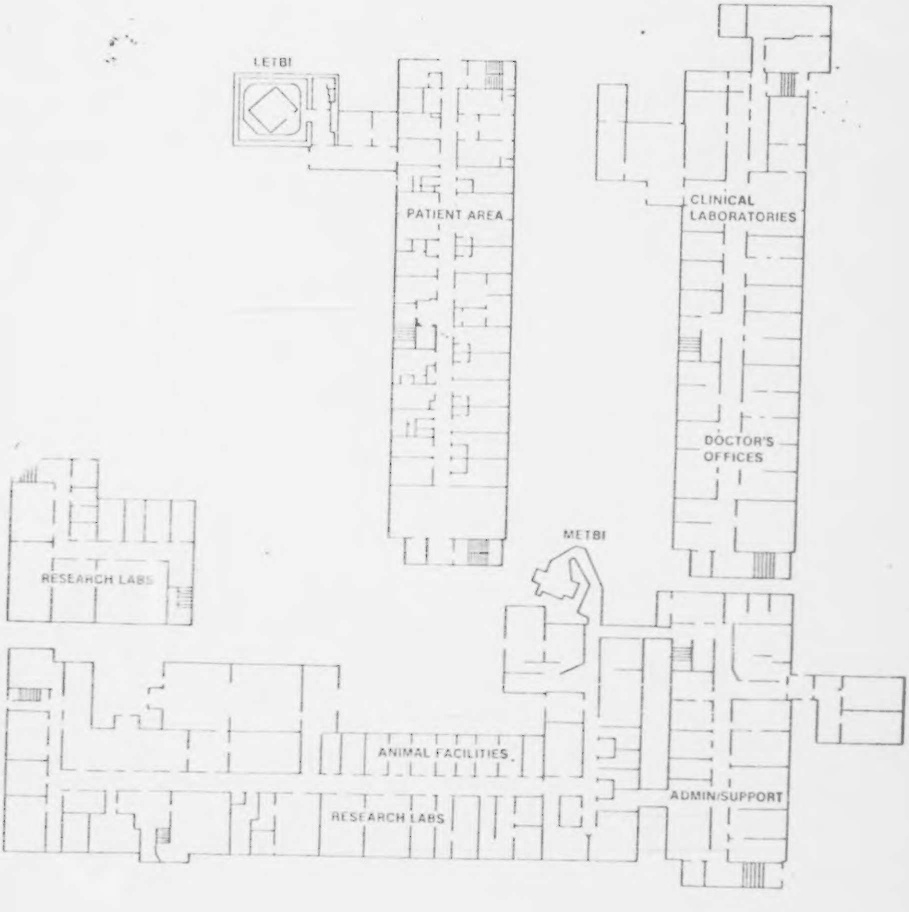
YEAR

FACILITIES 1940's—60's


PATIENT AREA
OAK RIDGE
HOSPITAL
CLINICAL
LABORATORIES
DOCTOR'S
OFFICES
RESEARCH LABS
RESEARCH LABS
PATIENTS
ADMIN/SUPPORT
ORINS

FACILITIES IN 1968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PATIENT AREA
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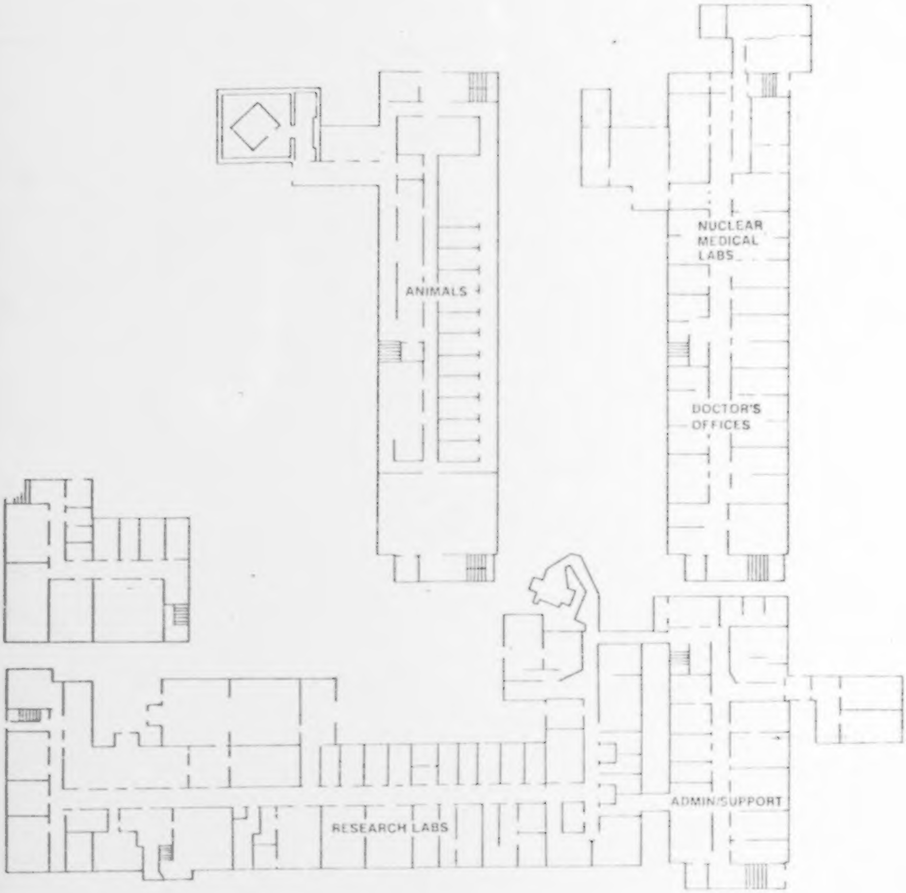
DOCTOR'S OFFICES
METBI
RESEARCH LABS
ANIMAL FACILITIES
RESEARCH LABS
ADMIN/SUPPORT

PRESENT FACILITIES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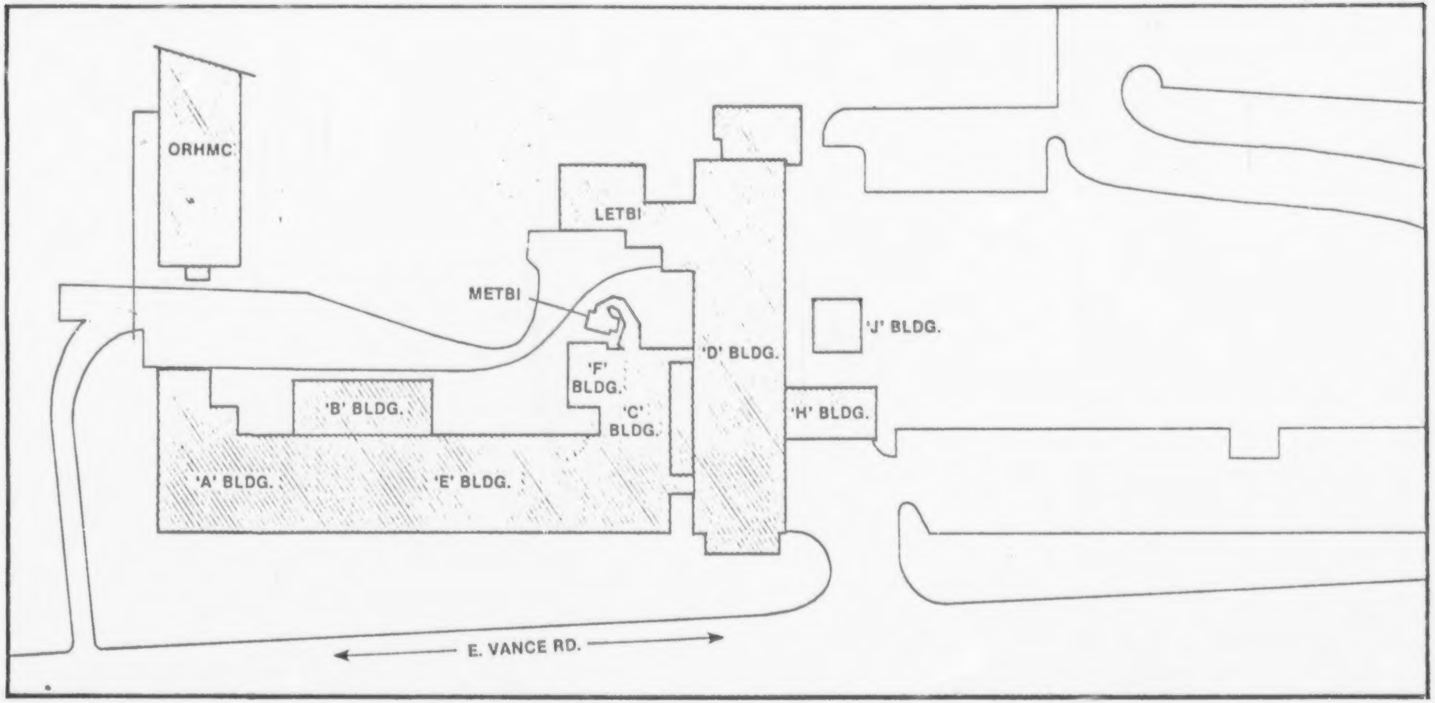
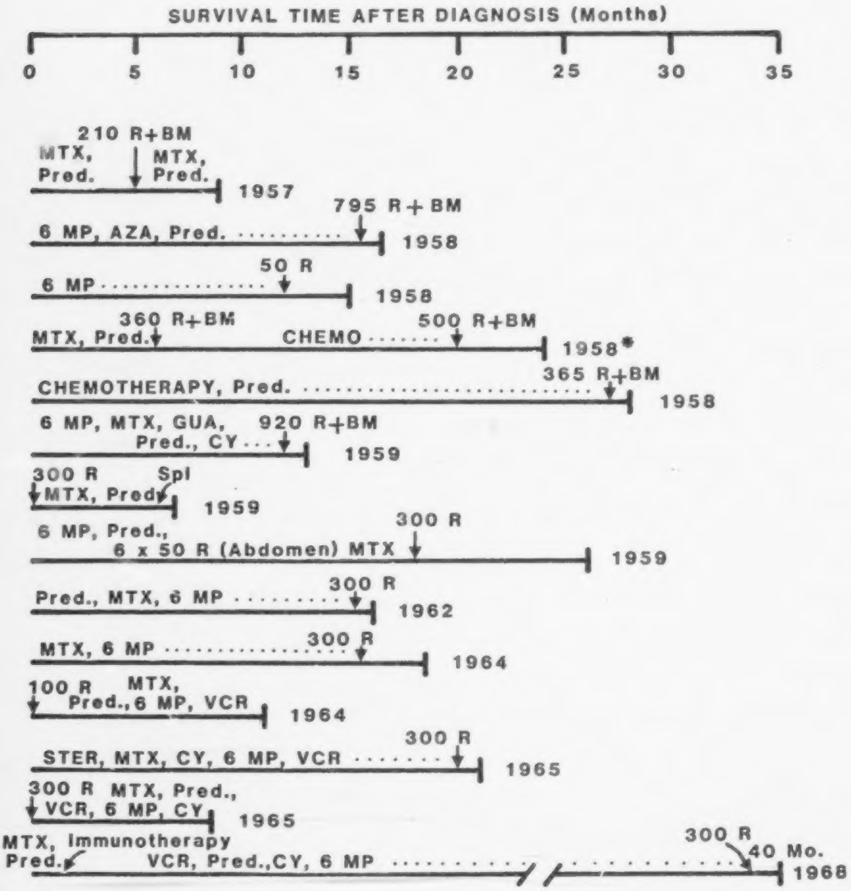
ANIMALS
DOCTOR'S OFFICES
ADMIN/SUPPORT
RESEARCH LABS


ORHMC
LETBI
METBI
'J' BLDG.
'D' BLDG.
'F' BLDG.
'B' BLDG.
'C' BLDG.
'H' BLDG.
'A' BLDG.
'E' BLDG.
E. VANCE RD.

OVERALL SITE PLAN

ACUTE LYMPHATIC LEUKEMIA

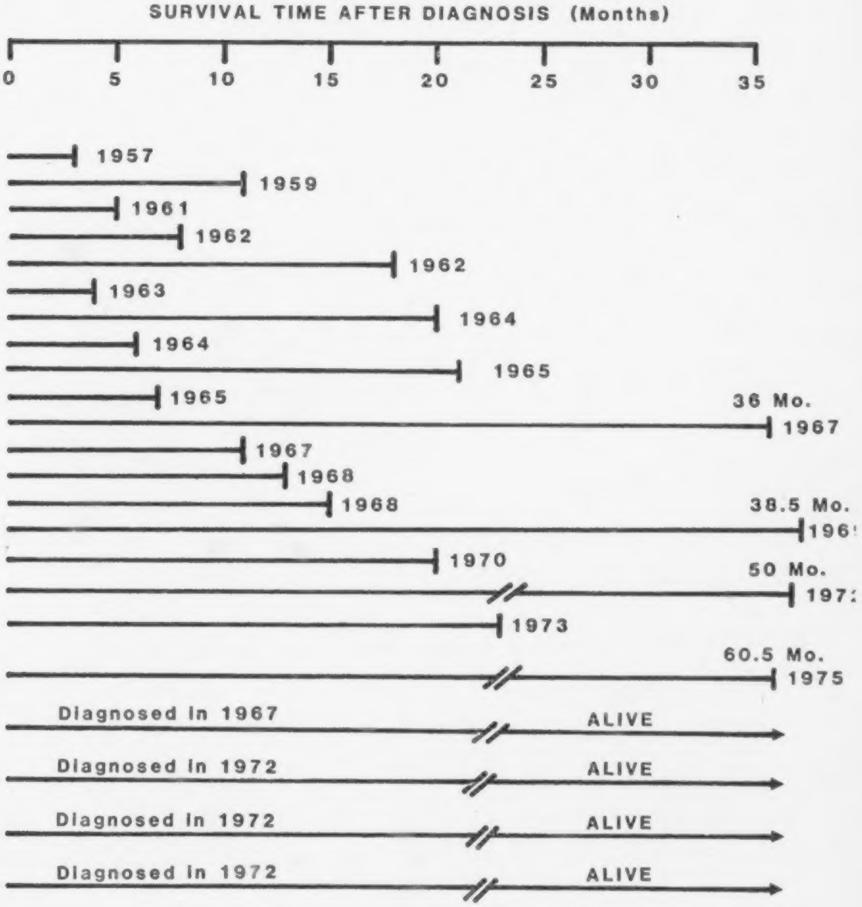
CHILDREN TREATED WITH METBI AND CHEMOTHERAPY AT ORINS



* Acute Primitive Cell Leukemia

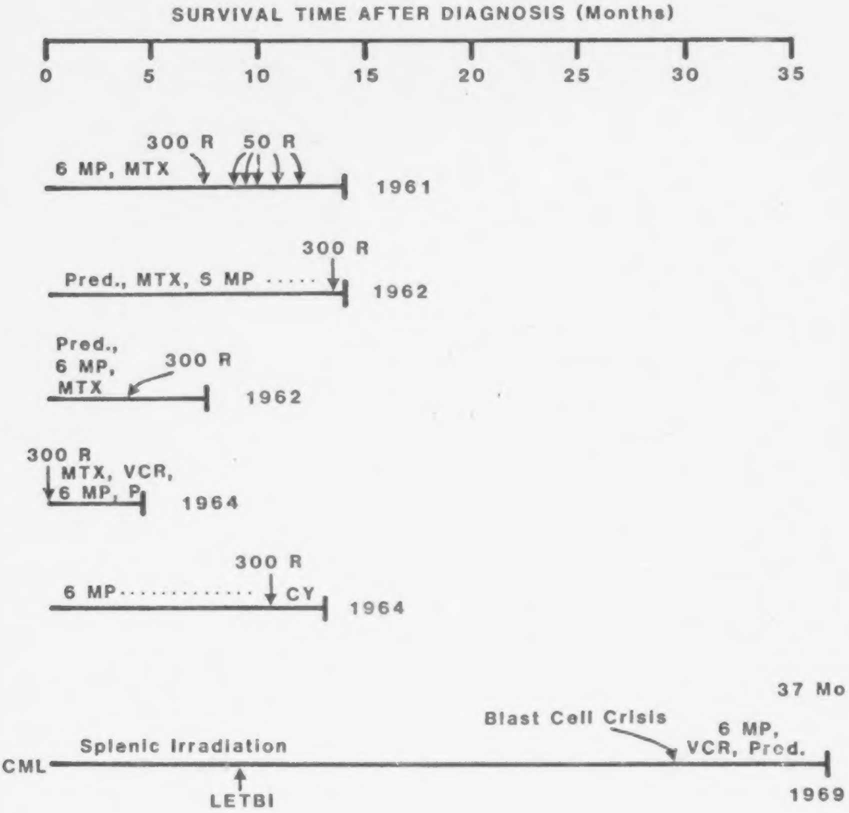
ACUTE LYMPHATIC LEUKEMIA

CHILDREN TREATED WITH CHEMOTHERAPY AT ORINS/ORAU



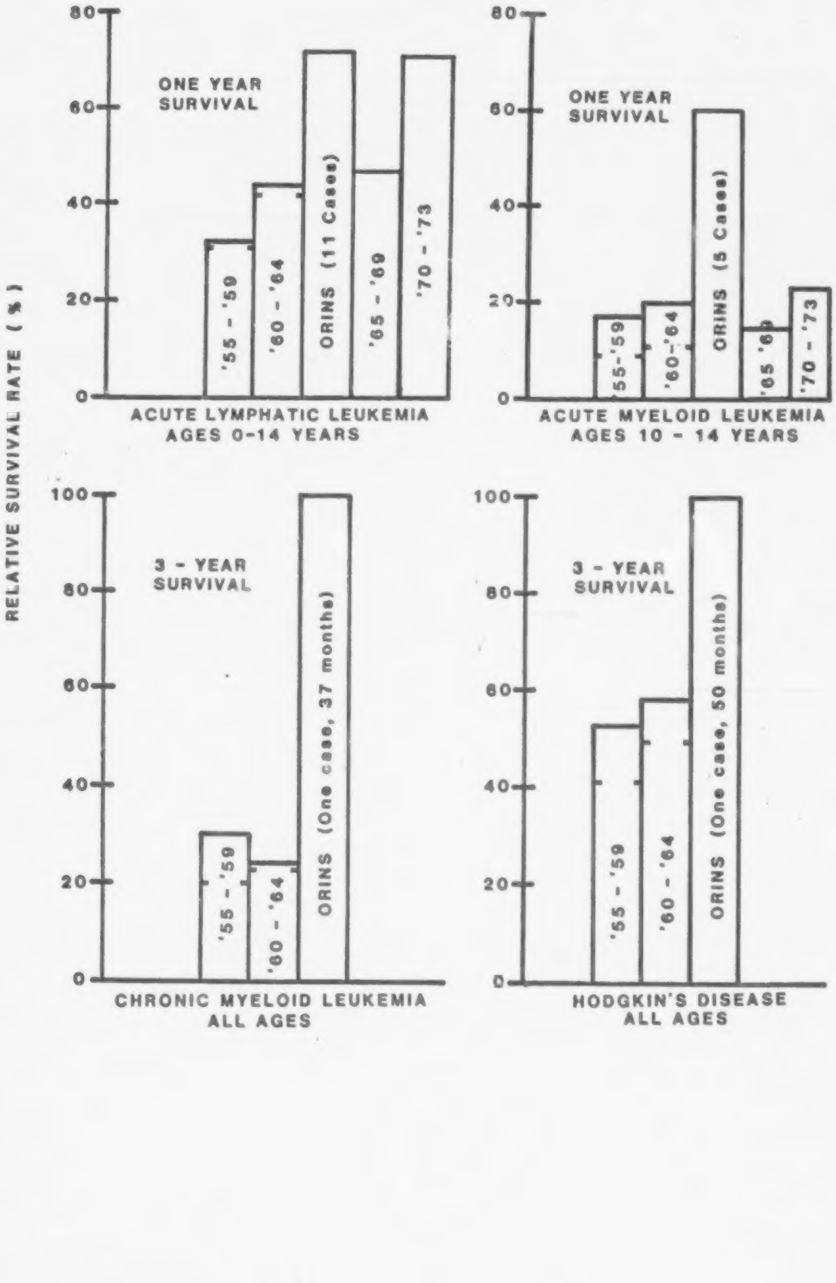
ACUTE MYELOID LEUKEMIA

CHILDREN TREATED WITH TBI AND CHEMOTHERAPY AT ORINS

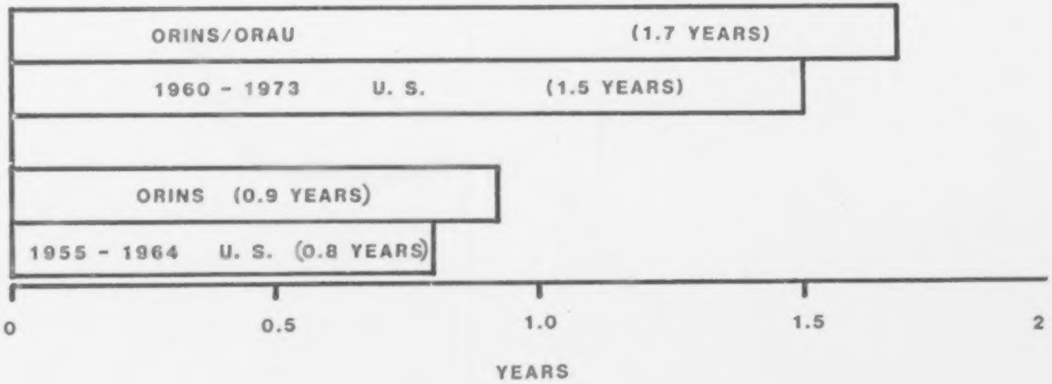


END RESULTS IN CANCER (US DHEW) IN OVER 100 U. S. HOSPITALS AND ORINS

Relative Survival Rates by Calendar Periods of Diagnosis



MEDIAN SURVIVAL TIME, ACUTE LYMPHOCYTIC LEUKEMIA
(< 15 YEARS) WITH "CONVENTIONAL" TREATMENT



[CANCER RESEARCH 27 Part 1, 2535–2540, December 1967]

Preliminary Trials of Clinical Immunotherapy[1]

G. A. ANDREWS, C. C CONGDON,[2] C. L. EDWARDS, N. GENGOZIAN,
B. NELSON, AND H. VODOPICK

Oak Ridge Associated Universities, Oak Ridge, Tennessee

SUMMARY

An attempt was made to achieve therapy of incurable malignant disease by means of lymphocytes from the thoracic ducts of homologous donors specifically sensitized with malignant cells. Of two attempts to treat acute leukemia, one was technically satisfactory but failed to show a distinct therapeutic effect. In the other, technical difficulties reduced the number of lymphocytes obtained; the procedure was otherwise without incident and failed to influence obviously the course of the disease.

One patient with malignant melanoma was given lymphocytes from a nonsensitized donor, with no apparent effect. Another patient with this disease was given lymphocytes from a sensitized donor and had a fatal outcome that may have represented a graft-against-host reaction.

EXPERIMENTAL PROCEDURE

We made preliminary trials of treatment of acute leukemia and malignant melanoma by the infusion of lymphocytes obtained from the thoracic duct lymph of specifically sensitized donors. Basing this trial on the work of Delorme and Alexander (4), we wanted to test the possibility that the sensitized lymphocytes would exert an antitumor effect, augmenting that of prior conventional therapy.

The general plan of our experiments was as follows: Patients with incurable disease were selected on the basis of (*a*) availability, by marrow aspiration or biopsy, from the patient of a considerable number of malignant cells relatively free from normal cells; and (*b*) willingness and availability of a family member or other suitable volunteer to serve as a sensitized donor. The emotional stability of the family and of the prospective donor was carefully considered. Hazards, especially those to the donor, were discussed in detail with the potential donor.

The leukemic or neoplastic cells were obtained from the patient, irradiated *in vitro* to render them incapable of propagation, and injected intramuscularly and subcutaneously into the potential donor. Then appropriate chemotherapy was given to the patient. After a period of 2 weeks or longer, the thoracic duct of the volunteer donor was cannulated and lymph was allowed to drain continuously for as long as 4 days. Every 3 hours the collected lymph was centrifuged, and the cells, with accompanying lymph fluid, were given intravenously to the patient. Most of the supernatant liquid portion was reinfused into the donor. Appropriate clinical and laboratory observations were made on the patient and donor.

In two patients, one with acute leukemia and one with metastatic malignant melanoma, we were able to complete this sequence as planned. To another patient we gave thoracic duct lymphocytes from a donor who had received no sensitizing cells. In a fourth attempt, the cannula in the thoracic duct of the sensitized donor became obstructed in 1 day and only a small number of lymphocytes could be obtained. These last two studies are included in the present report because they contribute information on certain aspects of the study and on the problems encountered. The data for all four studies are summarized in Table 1.

The thoracic duct cannulation was done under local anesthesia. Cream was given preoperatively to help visualize the duct. In our first trial, we gave the donor milkshakes postoperatively to stimulate the flow of lymph; however, it proved difficult to visualize the separation of lymphocytes from the opaque fluid and therefore the donors subsequently were strictly limited in milk and milk products. Thoracic duct lymph, which contains fibrinogen and other clotting factors and will congeal on standing, was collected directly from the cannula tubing into sterile blood donor units containing anticoagulant. In Cases P-1 and P-4, the containers were kept under refrigeration, and in Cases P-2 and P-3 at room temperature. Refrigeration, although helping to reduce growth of any accidentally introduced microorganisms, might result in a more rapid loss of immunologic properties of lymphocytes than would occur at room temperature (2). Rigid sterile precautions were maintained throughout the collecting and processing of lymph. Plastic bags commercially prepared to receive blood donations and containing acid-citrate-dextrose solution were initially used (Cases P-1 and P-4) because of their convenience, but there were difficulties after centrifugation in visualizing the line of demarcation between the lymphocyte button and the milky supernatant lymph. Glass blood-donor bottles containing 25 ml of 5% dextrose-water with 200 units of phenol-free heparin (Upjohn Company) used in Cases P-2 and P-3 provided a clearer separation. The lymph was collected by gravity without vacuum. Each 3-hour collection, which varied from a few milliliters to over 200 ml, was centrifuged for 30 minutes at 200 × *g*. The supernatant fluid was aspirated through a long needle into a 250-ml vacuum blood-collecting unit. The sedimented lymphocytes were not washed but were resuspended in 25 to 50 ml of residual donor lymph and given intravenously at a moderate rate to the patient. At the end of the collection period, we clamped off the cannula and left it in place for at least 72 hours to allow the lymph to clot. The tube was then pulled out, and a sterile pressure dressing was applied.

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[1] From the Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee, under contract with the U.S. Atomic Energy Commission.

[2] Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

Chart 1 shows the effects of the procedure on the leukocyte and lymphocyte counts of the donors. The changes are quite variable but not profound; perhaps there is a tendency toward lymphopenia during withdrawal of the lymph.

Chart 2 shows similar data for the recipients. Here the effect is obscured by therapy with nitrogen mustard. Certainly, there is no obvious rise in circulating lymphocytes as a result of the infusion except, possibly, in Patient P-1.

TABLE 1

Summary of Information on Four Therapeutic Trials

	Patient P-1: acute leukemia	Donor D-1	Patient P-2: metastatic malignant melanoma	Donor D-2	Patient P-3: acute leukemia	Donor D-3	Patient P-4: metastatic malignant melanoma	Donor D-4
Sex	M	F	M	F	F	M	M	M
Relationship		Mother		Mother		Father		Uncle
Blood type	O+	O+	A−	O+	O−	O−	A+	A+
Previous blood transfusions	None	None	None	None	2 units packed cells	None	None	None
Immunizing cells	Marrow aspiration	19 × 10⁸ (90% lymphoblasts)	Lymph node biopsy	1.9 × 10⁸		30.4 × 10⁸ lymphoblasts		No sensitization
Irradiation dose		10,000 R		20,000 R		10,000 R		
Anticoagulant		Heparin		Heparin		Heparin		
Environment		Ice bath		Room temperature		Ice bath		
Route of injection		3 i.m.		4 i.m. 2 s.c.		6 i.m. 4 s.c.		
Medication of patient after tissue taken for immunization	Prednisone 60 mg/day until Day −1, gradually reduced, stopped Day 11 Methotrexate 2.5 mg until Day −1.		Nitrogen mustard Days −1 and −2; total 0.4 mg/kg		Prednisone 40 mg/day; gradually reduced and stopped Day −6. Methotrexate 2.5 mg/day; on Day −14, changed to 15 mg i.m. approx. 2 times/wk.		Nitrogen mustard 0.3 mg/kg on Day −1.	
Interval from "sensitization" to thoracic duct cannulation		18 days		27 days		84 days		
Duration of cannulation		4 days		4 days		1 day		4 days
Anticoagulant		ACD[a]		Heparin in 5% dextrose		Heparin in 5% dextrose		ACD
No. of cells infused	1.4×10^{10}		21.9×10^{10}		0.4×10^{10}		1.7×10^{10}	
Amount of lymph infused (ml fluid)	2013		887		215		1935	

The first day of thoracic duct cannulation is taken as 0.

[a] ACD, acid citrate dextrose.

[b] Incubated for 1 hr at 37°C with leucine-^{3}H.

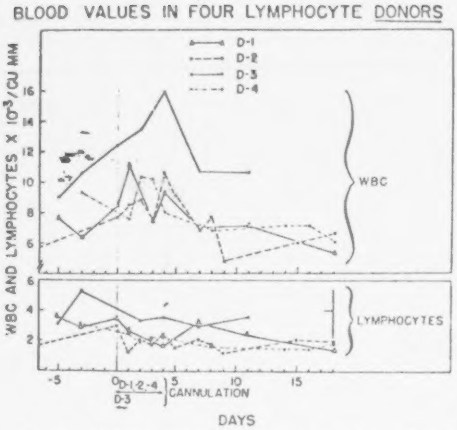

CHART 1. Leukocyte and lymphocyte values of donors during period of cannulation of thoracic duct and withdrawal of lymphocytes.

Case 1

This study has been previously reported (5). A three-year-old boy (P-1) with recently diagnosed, untreated acute leukemia on August 5, 1965, was given a general anesthetic for marrow aspiration from multiple sites in the posterior ilia. A total of 20 ml of bloody material was obtained containing approximately 2 billion nucleated cells of which over 90% were identified as lymphoblasts. These cells were promptly irradiated *in vitro* without supplemental oxygen to a dose of 10,000 R and injected intramuscularly into the patient's mother (D-1). The patient was given methotrexate 2.5 mg/day and prednisone 40 mg/day for 17 days, after which the methotrexate was discontinued and the prednisone was decreased gradually and finally stopped on the 29th day. At the time the methotrexate was stopped, the bone marrow was extremely hypocellular and blood values suggested that the patient was going into remission.

On the 18th day after she had received the leukemic cells, the patient's mother had her thoracic duct cannulated, and for the next 4 days her lymphocytes were infused into the patient. The patient received these without reaction. The clinical and hematologic course is summarized in Chart 3. On the 27th day after the beginning of the infusions he developed a transient, unexplained rash. A complete clinical and hematologic remission developed and lasted for 15 weeks without further therapy. There was then an exacerbation of the disease, which responded to appropriate chemotherapy. At 20 months after the initial treatment, the child was doing well on continued drug therapy and the mother was clinically well.

Case 2

A 45-year-old man (P-2) was admitted to the hospital in October, 1966. In 1961, a mole on the left side of his back, just above the iliac crest, had increased in size and turned black. It was excised and after it was reported to be a malignant melanoma a wider excision of the area was done. The patient remained well until July, 1966, when he developed throat irritation. A month later, his physician found a mass in the region of the left tonsil which on biopsy proved to be metastatic malignant melanoma and which was considered inoperable. He developed increasing difficulty in speaking and swallowing and began to lose weight.

Physical examination showed a lobulated dark mass in the left tonsillar region, extending down into the throat. There were lymph nodes in the left side of the neck as large as 3 x 3 cm.

After appropriate preliminary steps we decided to undertake an immunotherapeutic trial. On November 15, under general anesthesia, two large left cervical nodes were removed. The tissue, consisting almost entirely of metastatic melanoma, was minced and the cells were suspended in tissue culture fluid (Tc 199) and exposed *in vitro* to 20,000 R of gamma radiation. They were then injected intramuscularly and subcutaneously into the patient's mother (D-2), a healthy 67-year-old woman.

On the 27th day after the mother had received the tumor cells, the treatment of the patient with her lymphocytes was undertaken. On the two preceding days the patient had been given i.v. nitrogen mustard to a total dose of 0.4 mg/kg. The mother tolerated the procedure well; there was a distinct fall in the percentage of lymphocytes of her blood during this period. Approximately 48 hours after he had received the first lymphocyte infusion the patient developed fever, which became increasingly severe. On the day the infusions were terminated (4th day), the temperature reached 40.4°C. There was an accentuated anorexia, malaise, and occasional mild chills. Cultures were obtained from blood, urine, and throat; only the latter was positive, showing β-hemolytic streptococcus. Treatment with aqueous procaine penicillin was started. The patient had received penicillin in the past without reaction. By the following day he had a maculo-

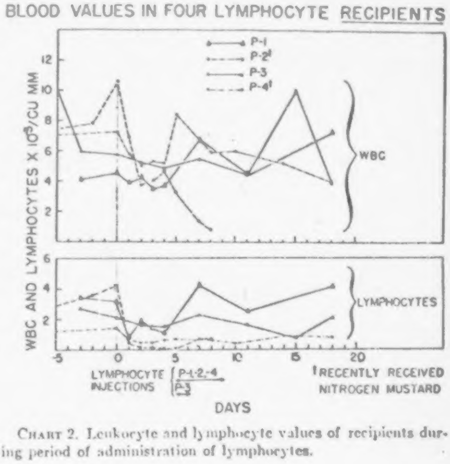

CHART 2. Leukocyte and lymphocyte values of recipients during period of administration of lymphocytes.

papular rash over the trunk and extremities. His general condition deteriorated. He developed diarrhea and became comatose; high fever persisted, and on the ninth day after the beginning of the lymphocyte infusion he died. Cytogenetic studies showed that 2 days before the patient's death, more than half of the lymphocytes in his blood were female.

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Autopsy showed metastatic malignant melanoma in the oropharynx, lymph nodes, intestines, liver, adrenals, bones, heart, and brain. Most of the metastases were small and they did not account for the patient's death. Infiltrations of lymphocytes and pyknotic nuclear remnants were seen in the dermis and epidermis. Similar infiltrations and microscopic foci of necrosis were found in the liver, adrenals, spleen, and lymph nodes. The lymph nodes and spleen had a pronounced depletion of lymphocytes, with much phagocytosis of red cells and nuclear debris. The marrow was partly replaced by multiple metastases, and hemopoiesis was severely depressed in the areas without neoplasm. No necrosis or lymphocytic infiltration were seen in the neoplasm. The malignant cells were much less cohesive than in the recent biopsy, appearing as rounded individual cells rather than as sheets of polygonal cells.

The histologic changes are consistent with an accelerated, accentuated immunologic reaction although this interpretation was made tentative by the considerations that the skin changes might have been caused by a penicillin reaction and the lymphoid and hemopoietic atrophy could be attributed, at least in part, to the nitrogen mustard.

Case 3

The patient (P-3) was a 4½-year-old girl with acute lymphoblastic leukemia. Her disease had been symptomatic for only 4 weeks. The diagnosis was made on the basis of circulating blasts with anemia and confirmed by examination of the marrow aspirate. Experimental treatment was undertaken in May, 1966. The patient's father (D-3), a 37-year-old man, volunteered to serve as a donor of thoracic duct lymphocytes. Under general anesthesia, 4.69×10^9 of the patient's bone marrow cells were aspirated from multiple sites. The cells were then irradiated with 10,000 R from a cesium-137 source and 3.0×10^9 of them were injected subcutaneously and intramuscularly at multiple sites to the donor. The donor experienced no complications or reactions to the injections.

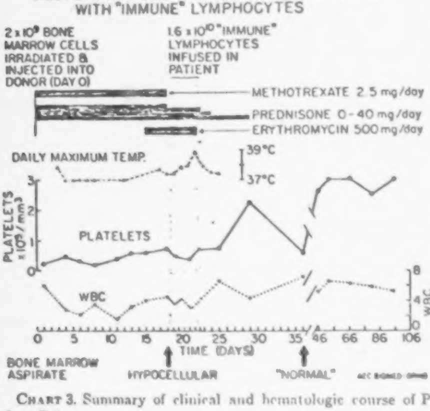

CHART 3. Summary of clinical and hematologic course of Patient P-1.

Several weeks were required for the patient to overcome an incidental infection and to develop a complete drug-induced remission, which we desired to establish before giving the lymphocytes. Eighty-four days after he had received the irradiated cells, the donor's thoracic duct was cannulated under local anesthesia. Although the donor tolerated the procedure well and a good flow of lymph was established initially, the cannula apparently was inadvertently pulled from the thoracic duct and the lymph collections were discontinued after recovery of only 4×10^9 cells (24 hours). The patient received these cells without incident. The donor's surgical wound healed without complication.

The patient was continued on maintenance intermittent (twice weekly) methotrexate therapy and had a satisfactory course until her leukemic process relapsed seven months later. She was then given vincristine sulfate and prednisone in an attempt to induce another remission, but she suddenly developed a severe pneumonic infection and died. At autopsy the cause of death was found to be an overwhelming infection with *Pneumocystis carnii*. There was no evidence of any beneficial or deleterious effect from the lymphocyte infusions.

Case 4

This 27-year-old man (P-4) was thought to have been in good health until three months before admission when he first noted multiple subcutaneous nodules. The diagnosis of disseminated malignant melanoma was based upon histologic examination of one of these nodules. At the time of admission in August, 1965, he had nausea, vomiting, considerable weight loss, and evidence of an abdominal mass.

A healthy 32-year-old uncle (D-4) volunteered to serve as a donor of thoracic duct lymphocytes to be infused into the patient. No attempt was made to sensitize the donor or his lymphocytes to the patient's tumor. The patient received 0.3 mg/kg of nitrogen mustard intravenously 1 day before beginning to receive the donor's lymphocytes. The lymphocytes obtained from the donor were incubated 1 hour at 37°C with tritiated leucine to label them before infusion into the patient. No reaction was witnessed. Serial biopsies of subcutaneous nodules failed to exhibit histologic evidence of any local effect of the lymphocyte infusion.

The donor tolerated the cannulation poorly and complained of considerable pain at the operative site. Because the supernatant lymph containing tritium could not be returned to the donor, he was given fresh frozen plasma during the period of lymphophoresis to replenish plasma protein, fibrinogen, and other coagulation factors. On the fourth day the cannula was clamped and 3 days later it was pulled from the wound without difficulty. The donor returned 3 days later with 400 ml of lymph accumulated under the skin at the operative site. The wound was opened and allowed to drain. Drainage continued for 4 days and stopped spontaneously. He also had a chylous pleural effusion removed by thoracentesis. He returned 2 weeks later with a febrile illness and a persistent left pleural effusion. No organisms could be cultured from the thoracentesis fluid, but he was given antibiotic therapy and recovered without further difficulty.

The patient's disease showed no response to the immunotherapy and progressed rapidly in spite of addition of chemotherapy and external radiation treatment. He died 2 months later of widely disseminated malignant melanoma. Autopsy showed no changes that were believed related to the immunotherapeutic attempt.

DISCUSSION

Delorme and Alexander (4) have shown a specific antitumor effect of transfused allogeneic lymphocytes in rats having fibrosarcoma; the antitumor effect can be enhanced by presensitizing the donor of the lymphocytes to the specific tumor. That this phenomenon might be exploited for treatment of human neoplasm seemed reasonable in light of the evidence for specific tumor antigenicity and immunologic factors in the control of human neoplastic disease. Woodruff and Nolan (20) reported an apparent antitumor effect from nonsensitized splenic lymphocytes given to patients with malignant melanoma.

Critical to our experiment were (*a*) the availability of a substantial number of neoplastic cells with which to immunize a donor, and (*b*) a disease in which the amount of tumor remaining in the patient at the time of infusion was minimal. Acute childhood leukemia was thought to fill these criteria, and special examples of neoplasms in adults might be equally suited.

It has generally been impossible to transmit solid tumors or leukemia into homologous recipients (16, 18), although a few exceptions have occurred (14), especially in instances in which the recipient of a cancer-bearing kidney graft has been given immunosuppressive therapy (reviewed in Ref. 6). To make the procedure more acceptable, we sought an extra margin of safety for the intended donor of lymphocytes by irradiating the malignant cells that were to be injected for the purpose of sensitization. The dose of 10,000 R or more is thus given to prevent possible proliferation in the donor. What effect this irradiation may have on the specific antigens of the tumor or leukemia still is not known. The possibility that there could be changes in the antigens is suggested by the reports by Luzzio *et al.* (9, 10), although their work was with serum protein rather than cellular antigens and therefore cannot be applied directly to the present problem. They irradiated human serum proteins *in vitro* and *in vivo* with doses as low as 100 and 200 rads and noted a specific alteration in the combining capabilities of these proteins with an immune serum prepared against X-irradiated (1.3×10^6) human γ-globulin. In view of this information, it may be desirable to seek a milder treatment, such as freeze-thawing, to achieve the killing effect on the cells to be used for sensitization.

Cannulation of the thoracic duct has been developed elsewhere, independent of these studies, as a method of removing large quantities of osmotic fluid for therapy of anasarca due to heart failure, hepatic disease, and renal disease (13). It has also been used in an attempt to suppress the immune response by removing immunoglobulins and immune competent cells (19).

Comparing the two patients (P-2 and P-1) in whom the entire procedure was completed as planned, we note that the lack of any pronounced reaction in Patient P-1 is in sharp contrast with the acute and overwhelming reaction in Patient P-2. Although Patient P-2 had an extensive and obviously hopeless malignancy, his condition worsened very rapidly after the lymphocyte infusion, and the features at autopsy were compatible with those of a graft-*versus*-host reaction. The presence of predominantly female lymphocytes in the blood 2 days before death tends to support this possibility. Interpretation of the patient's clinical course is made difficult by the possible influence of nitrogen mustard therapy and the fact that he may have had a penicillin reaction. Although he was known to have received penicillin before without incident, this does not exclude a severe, generalized penicillin reaction. Clinically, there was little similarity to the usual forms of penicillin-induced dermatitis medicamentosa.

The devastating reaction experienced is thought to be the result of a graft-*versus*-host reaction, resulting from the cytotoxic effect of the sensitized lymphocytes against all the patient cells, normal and neoplastic. Although Patients P-4 and P-1 also received large numbers of lymphocytes (significantly less than P-2), neither had a significant reaction. They also differed from Patient P-2 in a number of ways: (*a*) Patient P-4 received lymphocytes from a nonsensitized donor; (*b*) Patient P-1 was receiving prednisone in small doses during the period of lymphocyte infusion; (*c*) the lymphocytes were collected under refrigeration for P-4 and P-1 while for P-2 the collections were made at room temperature (20°C); (*d*) in P-4 and P-1 the donor and the patient were of the same blood type while in P-2 the patient was A-negative and the donor O-positive.

The significance of major blood-group incompatibility differences between donor and recipient in homotransplantation studies is still not clear. In attempting to define the use of the lymphocyte transfer test for potential selection of donor and recipient for organ transplants, studies by Moorhead and Patel (11) and Nelson *et al.* (12) suggest that there is no correlation between ABO incompatibility and leukocyte antigen differences. In renal homografts, however, there appears to be a better chance of prolonged survival of the graft if donor and recipient are ABO-compatible (17). Levin *et al.* (8) and Schmidt *et al.* (15) have reported a most interesting case describing formation of an erythroid homograft in a Group O patient with acute leukemia after transfusion of leukocytes from a chronic myelocytic leukemia (CML) patient of Blood Group A. Within 48 days after transfusion, 85% of the red cell mass was Group A, and this in the presence of naturally occurring anti-A agglutinins of the recipient. Indeed, the graft appeared to flourish despite the incompatible antibody and the subsequent formation of immune anti-B, the latter representing a possible response to transfusion of Group AB blood given shortly after the CML leukocytes. A graft-*versus*-host reaction, "secondary disease," was not observed in the patient. The authors suggest that this was due to the relative paucity of lymphocytes in the transfused CML cells.

Alexander (personal communication) has suggested that the severe reaction in Patient P-2 may have been caused by humoral antibodies present in the donor's thoracic duct lymph, possibly induced in the donor by the small amount of lymphoid tissue included with the tumor used for sensitization. The failure to see this in Patient P-1 would be explained, then, by the assumption that the sensitizing cells included no significant number of lymphocytes or else the prednisone received by the recipient prevented the reaction. If a passive transfer of such antibodies were the cause of the severe reaction, it would obviously be important to wash the donor lymphocytes. Our reason for not doing so was to avoid trauma to them. We also thought that some beneficial humoral antitumor antibody might be carried in the included lymph.

In neither patient was there clear demonstration of an antitumor effect. In Patient P-1, the acute leukemia was already entering remission when the lymphocytes were given, and the remission lasted about as long as might have been expected in view of the fact that maintenance chemotherapy was not given. In Patient P-2, the only indication of a possible antitumor effect was the loss of cohesiveness of the tumor cells as seen in the comparison of autopsy with recent biopsy material. This change was definite but has not been shown to represent a cytotoxic effect or to have resulted from the lymphocytic infusion. Similar changes were not seen, however, in the tumor of Patient P-4 who also received nitrogen mustard and a comparable dose of lymphocytes, but from an unsensitized donor.

There is uncertainty about the optimal, immunologically effective time interval between sensitization of the donor and withdrawal of the lymphocytes. Studies in animals by Alexander *et al.* (1) suggest that the donor must be in the phase of immunization during which large numbers of pyroninophilic cells are produced; this is probably at the time of the early (2 to 3 days) dissociated growth of germinal centers described by Congdon and Goodman (3) after tissue homografting. The time course of this synchronized dissociated growth of immunologically competent cells is said to be dependent upon the amount of antigen (foreign tissue) administered, the genetic relationship of the antigen to the host, and the number of exposures to the antigen. Unfortunately, these are variables yet to be defined for man. It should be noted that in the series reported here the graft-*versus*-host reaction thought to have occurred in Patient P-2 came after the administration of cells obtained from the donor 27 days after sensitization.

We consider the hazards to the donor as the most serious obstacle to this type of experimental therapy and gave great consideration to them. One of our donors (for Patient 4) had a significant complication from the surgical procedure. Sensitization of the donor might cause some later difficulty if he were to serve as a donor or recipient of blood transfusions. We are concerned about the remote but catastrophic possibility that neoplasm could be induced in the donor, perhaps by a virus or other agent not sensitive to radiation in the doses used for *in vitro* treatment of thetumor. No long-term effects on the donors have as yet been manifest. All three who received irradiated neoplastic cells remain in good health without any indication of ill effects. No effort has been made to assess the psychologic effects of the experiment upon the donors. None have expressed any regret for their role in the study.

The moral aspects of this research have been given careful consideration and have caused us much concern. There are no generally accepted standards that we can refer to. The donors did not arrive at their decision to participate with the emotional detachment that is necessary for a true volunteer, that is, a person defined as offering himself without inducement, intimidation, promise or expectancy of favor, or threat of loss thereof, and void of all ulterior motive. Although we were careful not to exert coercion, the situation itself is inherently coercive. We have considered the fact that if an opportunity to "volunteer" is declined, this might also leave psychologic scars in the relative after the patient is dead. For this reason we have been selective in even broaching the subject.

In spite of these reservations, and in spite of the absence of evidence of benefit to the patients in these initial attempts, we believe that further cautious trials of this sort are justified, in view of the promising animal experiments and the technical feasibility of using thoracic duct lymphocytes.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Kong-oo Goh for cytogenetic studies and to Dr. Robert R. Bigelow and Dr. Ernest Hendrix who performed the thoracic duct cannulations.

REFERENCES

1. Alexander, P., Delorme, E. J., Hamilton, L. D. G., and Hall, J. G. Effect of Nucleic Acids from Immune Lymphocytes on Rat Sarcomata, Nature, *213:* 569-572, 1967.
2. van Bekkum, D. W. The Selective Elimination of Immunologically Competent Cells from Bone Marrow and Lymphatic Cell Mixtures. I. Effect of Storage at 4°C. Transplantation, *2:* 393-404, 1964.
3. Congdon, C. C., and Goodman, J. W. Changes in Lymphatic Tissues During Foreign Tissues Transplantation. *In:* A. P. Cristoffanini and G. Hoecker (eds.), Proceedings of the International Symposium on Tissue Transplantation, Aug 30-Sept. 2, 1961, pp. 181-207. Santiago, Chile: Universidad de Chile, 1962.
4. Delorme, E. J., and Alexander, P. Treatment of Primary Fibrosarcoma in the Rat with Immune Lymphocytes. Lancet, *2:* 117-120, 1964.
5. Edwards, C. L., Congdon, C. C., Gengozian, N., Vodopick, H., and Andrews, G. A. Treatment of Acute Leukemia: An Experimental Immunologic Approach. Exptl. Hematol., *9:* 23-24, 1966.
6. Hume, D. M. Renal Homotransplantation in Man. Ann. Rev. Med., *18:* 229-268, 1967.
7. Lanman, J. T., Bierman, H. R., and Byron, R. L., Jr. Transfusion of Leukemic Leukocytes in Man. Hematologic and Physiologic Changes. Blood, *5:* 1099-1113, 1950.
8. Levin, R. H., Whang, J., Carbone, P. P., and Freireich, E. J. Erythroid Homograft Following Leukocyte Transfusion in a Patient with Acute Leukemia. I. Clinical Studies and Implications. Blood, *26:* 587-596, 1965.
9. Luzzio, A. J. The Serologic Specificity of Radiation Altered Human Serum γ-Globulin. J. Immunol., *90:* 224-227, 1963.
10. Luzzio, A. J., Friedman, B. I., Kereiakes, J. G., and Saenger, E. L. Specific Proteins in Serum of Total-Body Irradiated Humans. J. Immunol., *96:* 64-67, 1966.
11. Moorhead, J. F., and Patel, A. R. Influence of Sex and ABO Blood Group on the Normal Lymphocyte Transfer Test. Brit. Med. J., *2:* 1111-1113, 1964.
12. Nelson, S. D., Bridges, J. M., and McGeown, M. G. Comparison of Lymphocyte-Transfer Test and White-Blood-Cell Grouping for Organ Donor Selection. Lancet, *1:* 1359-1362, 1965.
13. Sarles, H. E., Remmers, A. R., Hargest, T. S., Smith, G. H., and Artz, C. P. Observations Concerning the Extracorporeal Dialysis of Lymph in the Management of Chronic Renal Failure. New Engl. J. Med., *273:* 79-83, 1965.
14. Scanlon, E. F., Hawkins, R. A., Fox, W. W., and Smith, W. S. Fatal Homotransplanted Melanoma. Cancer, *18:* 782-789, 1965.

15. Schmidt, P. J., Yokoyama, M., McGinniss, M. H., and Levin, R. H. Erythroid Homograft Following Leukocyte Transfusion in a Patient with Acute Leukemia. II. Serologic and Immunochemical studies. Blood, *26:* 597-609, 1965.
16. Southam, C. M. Homotransplantation of Human Cell Lines. Bull. N. Y. Acad. Med., *34:* 416-423, 1958.
17. Starzl, T. E., Marchioro, T. L., Holmes, J. H., Hermann, G., Brittain, R. S., Stonington, O. H., Talmage, D. W., and Waddell, W. R. Renal Homografts in Patients with Major Donor-Recipient Blood Group Incompatibilities. Surgery, *55:* 195-200, 1964.
18. Thiersch, J. B. Attempted Transmission of Acute Leukemia from Man to Man by the Sternal Marrow Route. Cancer Res., *6:* 695-698, 1946.
19. Tunner, W. S., Carbone, P. P., Blaylock, W. K., and Irvin, G. L., III. Effect of Thoracic Duct Lymph Drainage on the Immune Response in Man. Surg. Gynecol. Obstet., *121:* 334-338, 1965.
20. Woodruff, M. F. A., and Nolan, B. Preliminary Observations on Treatment of Advanced Cancer by Injection of Allogeneic Spleen Cells. Lancet, *2:* 426-429, 1963.

EXPERIMENTAL HEMATOLOGY

No. 9: 1966

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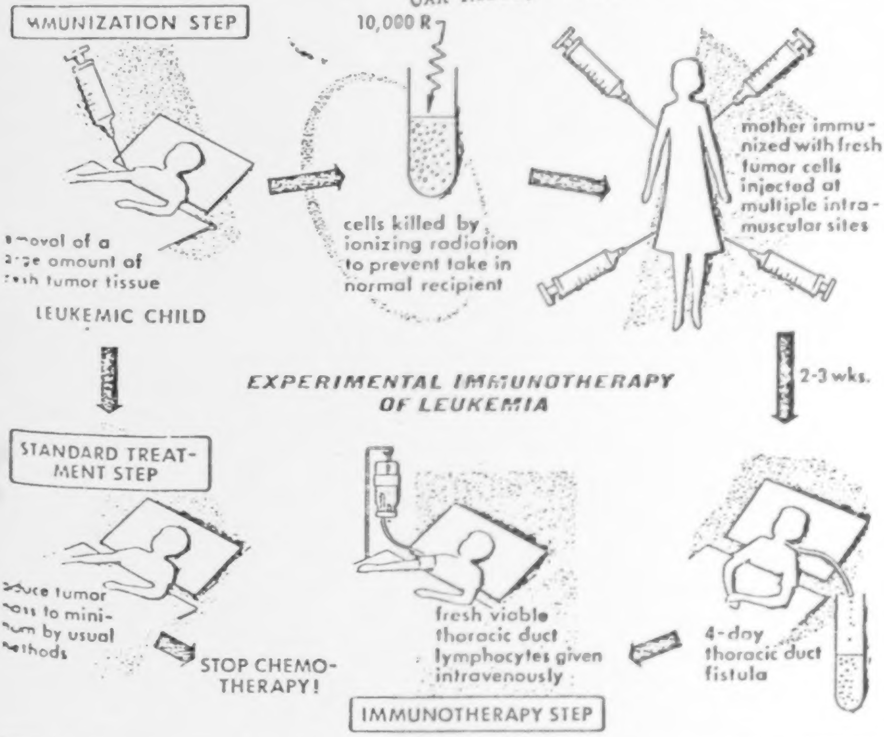
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BIOLOGY DIVISION
OAK RIDGE NATIONAL LABORATORY

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III. Immunotherapy of Cancer and Immunocompetent Cells

TREATMENT OF ACUTE LEUKEMIA: AN EXPERIMENTAL IMMUNOLOGIC APPROACH

C. L. Edwards, C. C Congdon, N. Gengozian, H. Vodopick, and G. A. Andrews

From the Oak Ridge Institute of Nuclear Studies, and Biology Division,
Oak Ridge National Laboratory, Oak Ridge, Tenn.

This is a report of an attempt at immunotherapy of acute leukemia in a 3-year-old boy. The protocol was designed to test for a therapeutic effect of "immunized" thoracic duct lymphocytes in human leukemia analogous to the effect demonstrated for isologous hematopoietic tissue in murine leukemia[1] and homologous and heterologous immune lymphocytes in certain murine tumors.[2,3] Our specific protocol in the present case was based on the work of Delorme and Alexander.[4]

After explaining in detail the rationale and nature of the experimental method to the parents, two billion nucleated cells (more than 90% lymphoblasts) were aspirated from the patient's bone marrow and irradiated with 10,000 R from a ^{137}Cs source. The irradiated cells were injected intramuscularly into the donor (patient's mother). The patient was then treated with methotrexate (2.5 mg) and prednisone (40 mg/day) for 17 days, after which the methotrexate was discontinued and the prednisone was decreased at increments of 10 mg/day every 3 days. On the 18th day the donor's thoracic duct was cannulated; the lymph was collected in a refrigerated plastic blood receptacle containing ACD solution; and at 3-hr intervals for 4 days the lymphocytes were harvested by centrifugation and infused into the patient. A total of 1.6×10^{10} cells was given.

At the onset of the infusion a bone marrow aspirate was hypocellular, but peripheral blood values indicated that the disease was going into remission. A hematologic remission was achieved and maintained for 15 weeks without further therapy. Bone marrow examination during the 16th week showed blast cells, and the patient was placed on vincristine and prednisone.

The anticipated possible hazards to the donor included: (1) an immediate or early sensitivity reaction to the injected bone marrow cells; (2) complications of the thoracic duct cannulation; (3) depletion of constituents of the thoracic duct lymph; and (4) (conceivably) the transmission of the leukemia. The patient's mother experienced no reaction to the injected cells. The thoracic duct cannulation was done under local anesthesia with only moderate postoperative discomfort and minimal disability. There was no quantitative depletion of circulating leukocytes or serum globulin, although there was a transient drop in the serum albumin. The leukemic cells were irradiated to assure nonviability, although efforts by others to transmit leukemia using viable cells have failed.[5]

The anticipated risks to the patient include: (1) an anaphylactoid or other immediate reaction to the infused lymphocyte suspension; (2) a graft-vs-host (secondary disease) reaction; and (3) deprivation of conventional chemotherapy. The patient experienced a mild febrile reaction not clearly due to the infusion during the infusion period, which was otherwise uncomplicated. The only symptom suggestive of a graft-vs-host reaction was a faint transient maculopapular rash in the 4th postinfusion week. Conventional chemotherapy was administered before the infusion to decrease the leukemic cell population against which the lymphocytes were to exert their effect. Maintenance therapy was withheld for 16 weeks to permit further observations after the experimental treatment.

Apparently the hazards of this procedure are sufficiently small to warrant further attempts. Modification of the protocol to delete prednisone during the infusion period is planned. Further in vitro testing for an elicited immune response is also planned.

References

[1] G. Mathé, "Secondary syndrome: A stumbling block to the treatment of leukemia by whole body irradiation and transfusion of allogenic hematopoietic cells," in *Diagnosis and Treatment of Acute Radiation Injury*, World Health Organization, International Documents Service, New York, 1961.

[2] M. F. A. Woodruff and M. O. Symes, "The use of immunologically competent cells in the treatment of cancer; experiments with a transplantable mouse tumor," *Brit. J. Cancer* 16(4), 707 (1962).

[3] M. F. A. Woodruff, M. O. Symes, and N. F. Anderson, "The effect of intraperitoneal injection of thoracic duct lymphocytes from normal and immunized rats in mice inoculated with Landshutz ascites tumor," *Brit. J. Cancer* 17(3), 482 (1963).

[4] E. J. Delorme and Peter Alexander, "Treatment of primary fibrosarcoma in the rat with immune lymphocytes," *Lancet* 2, 171 (1964).

[5] J. B. Thiersch, "Attempted transmission of acute leukemia from man to man by the sternal marrow route," *Cancer Res.* 6, 695 (1946).

APPENDIX 1

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TELEPHONE 483-8411

March 25, 1968

Maj. Gen. James W. Humphreys
Director of Space Medicine
National Aeronautics and Space
  Administration
Washington, D. C.

Dear Gen. Humphreys:

We are enclosing for your information and that of your staff two research proposals we are submitting to the Office of Biomedical Research, Manned Spacecraft Center, Houston. These proposed research programs are directly related to the studies we are already making for your office, but go beyond the scope of that task of determining the radiosensitivity of man.

We propose in one to exploit the observation we made with your support that power spectral analysis of pulmonary impedance signals seems to offer the physician, located remotely from his subject, a method of making medical interpretations of respiratory status more easily than those now available. In order to prove this, we need to study the effect of various physical stresses upon respiratory function of normal persons rather than cancer patients under radiotherapy. To do this job rapidly with modern technical facilities, we need to obtain financial support to rent an additional share of a small on-line computer that we are using part time now to aid in monitoring the patients in the AEC/NASA low-exposure rate irradiation facility (LETBI) with your funds. Since this study would share the use of personnel and physiologic monitoring equipment used in the study being done for you, we need the concurrence of your staff in its appropriateness. We feel this study will not slow the work on Task-109, but will augment and strengthen the meaning of our assessments in it of the effect of protracted radiation exposure on man.

In our other proposal, we suggest using the outer room of the LETBI facility to expose mice to a range of dose rates that bracket the limited one (1.5 R/hr) we are forced by therapeutic requirements to use with our patients at present. Such use of this facility to perform radiobiological experiments in animals is beyond the scope of our contracted task with your office. Such a study, though, would enable us to achieve an understanding of the effects of radiation protraction more rapidly, so we can use our human data obtained at one dose rate to help make predictions of effects at any rate that may be found subsequently in the course of space explorations. In it we hope to develop laboratory diagnostic systems in biochemistry and hematology that will aid the Lunar Receiving Laboratory to assess the extent of human radiation damage and its repair. The simultaneous irradiation of animals and men allowing interspecie comparisons is a unique opportunity that can only be done in this facility. These animal experiments will not interfere in any way with the on-going studies of patients receiving radiotherapy by protracted total-body irradiation. Any new findings in both blood morphology or biochemistry can be tested and applied at once to our human studies. The personnel to be involved in this animal study would be in addition to those already working on the human study. Dr. C. C. Lushbaugh will continue to direct and coordinate the entire program, but these additional studies will not dissipate his time significantly, since we have been able with the shift in emphasis from retrospective studies to prospective (on-going) human radiation studies to bring into this work several senior members of our clinical investigation group. We hope you will be able to concur with our opinion that these new projects would strengthen rather than weaken our investigations on man's radiosensitivity.

Dr. Lushbaugh and I are available to help you and your staff with any problems you may wish to discuss with us more fully.

Sincerely yours,

Gould A. Andrews

Gould A. Andrews, M.D.
Chairman
Medical Division

GAA:bbc

UNITED STATES GOVERNMENT

Memorandum

TO : John R. Totter, Director
Division of Biology and Medicine, HQ

DATE: September 22, 1967

FROM : S. R. Sapirie, Manager
Oak Ridge Operations

SUBJECT: ORAU STUDY OF THERAPEUTIC AND ACCIDENTAL WHOLE-BODY IRRADIATION FOR NASA (ORDER R-104(09), INTERAGENCY AGREEMENT 40-35-64)

OL:MJR

The enclosed program proposal (Schedule 189) has been submitted by ORAU to describe the scope of work and estimated cost proposed for continuation during Calendar Year 1968 of the studies for NASA to establish the radiosensitivity of man from human data obtained during therapeutic trials and from accidental exposure. The studies were initiated in June 1964, under NASA Order R-104, Task 9, and through Amendment 3, which provided funds in the amount of $300,000 during Calendar Year 1967, NASA has funded a total of $950,000 for these studies.

The ORAU CY 1968 proposed program has three objectives: (1) Completion of the retrospective study of human dose-response relations to various patterns of fractionated total-body irradiation; (2) completion of the retrospective study of the comparative incidence of deleterious physiologic responses when such fractionated exposures are made to restricted portions of the body instead of the total body; and (3) a steady growth in the on-going phase of this study to determine, by using the new low exposure total-body irradiation facility and its physiologic monitoring system, the tolerance of man to withstand radiation exposure rates of less than 2 R per hour for varying lengths of time.

The prospective studies are estimated to require NASA support for an operating cost level of $200,000 in CY 1968 as compared with $300,000 in CY 1967. Based upon the cost experience through June, and the funds remaining for the work through December 1967, it is not anticipated that any significant funds will be available for carry-over into CY 1968, and the full $200,000 will be required in new funds.

We believe the ORAU proposal is in accordance with AEC and NASA program plans and recommend your submission of the proposal to NASA for approval and issuance of an appropriate amendment to Order R-104, Task 9.

E G Wende
for S. R. Sapirie

Enclosure:
ORAU Proposal (6)

CC: S. G. English, HQ, w/encl.
R. C. Armstrong, w/encl.
C. W. Hill, w/encl.
N. A. Shearon, w/encl.
W. H. Henderson, w/encl.
H. M. Roth, w/encl.

SCHEDULE 189

ADDITIONAL EXPLANATION FOR OPERATING COSTS

OAK RIDGE OPERATIONS	40 04
FIELD OFFICE OR LABORATORY	BUDGET ACTIVITY NO.

1A.	CONTRACTOR: OAK RIDGE ASSOCIATED UNIVERSITIES, INC.	1B.	CONTRACT NO.: AT-(40-1)-GEN-33
2.	PROJECT TITLE: RADIOSENSITIVITY IN MAN: A STUDY OF THERAPEUTIC AND ACCIDENTAL WHOLE-BODY IRRADIATION NASA	3.	PROJECT NO.:
4.	STARTING DATE OF PROJECT: CONTINUING	5.	DATE SCHEDULE PREPARED: SEPTEMBER 1, 1967
6.	METHOD OF REPORTING: ANNUALLY	7.	WORKING LOCATION: OAK RIDGE, TENNESSEE
8A.	PERSON IN CHARGE: G. A. ANDREWS RALPH M. KNISELEY	8B.	PRINCIPAL INVESTIGATOR: G. A. ANDREWS, C. C. LUSHBAUGH, R. M. KNISELEY, C. L. EDWARDS, AND F. COMAS

		ACTUAL CY-1967	ESTIMATED CY-1968	ESTIMATED CY-1969
9.	MAN YEARS:	12.0	10.0	8.0
10.	COSTS:			
	PERSONAL SERVICES	$102,000	$ 76,000	$ 80,000
	TRAVEL	12,700	2,000	2,000
	MATERIALS AND SUPPLIES	20,000	2,000	2,000
	COMPUTER SERVICES (X-10, K-25)	17,000	5,000	5,000
	ORAU DATA PROCESSING	36,000	40,000	40,000
	EQUIPMENT	52,800	28,000	20,000
	TECHNICAL SERVICES	10,000	6,000	6,000
	DIVISION OVERHEAD	27,500	17,000	18,000
	ASSOCIATION OVERHEAD	40,000	24,000	27,000
		$318,000	$200,000	$200,000

11. DATES AND TITLES OF PUBLICATIONS:

OPEN LITERATURE REPORTS

A. LUSHBAUGH, C. C., HOFSTRA, R., ROTH, R. E., AND ANDREWS, G. A.: ED_{50} FOR GASTROINTESTINAL RESPONSES IN MAN. RADIATION RESEARCH 25, 114, MAY 1965 (ABSTRACT).

2. PROJECT TITLE: RADIOSENSITIVITY IN MAN: A STUDY OF THERAPEUTIC AND ACCIDENTAL WHOLE-BODY IRRADIATION

3. PROJECT NO.:

11. DATES AND TITLES OF PUBLICATIONS: (CONTINUED)

B. ANDREWS, G. A., AUXIER, J. A., AND LUSHBAUGH, C. C.: THE IMPORTANCE OF DOSIMETRY TO THE MEDICAL MANAGEMENT OF PERSONS ACCIDENTALLY EXPOSED TO HIGH LEVELS OF RADIATION. IN PERSONNEL DOSIMETRY FOR RADIATION ACCIDENTS, IAEA, VIENNA, AUGUST 1965.

C. LUSHBAUGH, C. C., COMAS, F., SAENGER, E. L., JACOBS, M.: RADIOSENSITIVITY OF MAN BY EXTRAPOLATION FROM STUDIES OF TOTAL-BODY IRRADIATION OF PATIENTS (INVITED LECTURE, FEBRUARY 15, 1966). RADIATION RESEARCH 27, 487-488, MARCH 1966.

D. ANDREWS, G. A.: TREATMENT OF RADIATION INJURY. J. MISSISSIPPI MED. ASSOC. 7, 534-538, 1966.

E. ANDREWS, G. A., LUSHBAUGH, C. C., AND KNISELEY, R. M.: PROCEEDINGS OF A PANEL ON EFFECTS OF TOTAL-BODY IRRADIATION IN THE HUMAN BEING. IAEA, VIENNA, MAY 17, 1966.

F. DALTON, C. P., AND CLOUTIER, R. J.: AN ARRANGEMENT OF RADIOACTIVE SOURCES FOR A LOW-EXPOSURE-RATE TOTAL-BODY IRRADIATION FACILITY. PHYSICS IN MEDICINE AND BIOLOGY 12, 116, 1967.

G. DALTON, C. P. AND CLOUTIER, R. J.: SOURCE ARRANGEMENT FOR A LOW-EXPOSURE-RATE TOTAL-BODY IRRADIATION FACILITY FOR MAN. USAEC REPORT ORINS-52, MAY 1, 1967, 205 PAGES.

H. FANGER, H., AND LUSHBAUGH, C. C.: RADIATION DEATH FROM CARDIOVASCULAR SHOCK FOLLOWING A CRITICALITY ACCIDENT: REPORT OF A SECOND DEATH FROM A NEWLY DEFINED HUMAN RADIATION DEATH SYNDROME. ARCH. PATH. 83, 446-460, MAY 1967.

I. LUSHBAUGH, C. C.: EDITORIAL, RADIATION AND SHOCK. JAMA 200, 181, 1967.

J. LANGHAM, W., EDITOR: SPACE RADIATION STUDY PANEL: RADIOBIOLOGIC FACTORS IN MANNED SPACE FLIGHT. JULY 1, 1967.

(1) LUSHBAUGH, C. C., ANDREWS, G. A., AND LANGHAM, W.: PRODROMAL RESPONSE, P. 76-90.

(2) CONRAD, R., ANDREWS, G. A., AND LANGHAM, W.: HEMATOLOGIC EFFECTS, P. 90-105.

(3) LANGHAM, W., AND LUSHBAUGH, C. C.: EARLY LETHALITY, P. 105-124.

(4) THOMPSON, J., AND ANDREWS, G. A.: CHEMICAL AND BIOLOGICAL PROTECTION, P. 218-230.

K. LUSHBAUGH, C. C., COMAS, F., AND HOFSTRA, R.: CLINICAL STUDIES OF RADIATION EFFECTS IN MAN: A PRELIMINARY REPORT OF A RETROSPECTIVE SEARCH FOR DOSE-RESPONSE RELATIONSHIPS IN THE PRODROMAL SYNDROME. RADIATION RESEARCH. SUPPL. 7, ____, 1967.

2. PROJECT TITLE: RADIOSENSITIVITY IN MAN: A STUDY OF THERAPEUTIC AND ACCIDENTAL WHOLE-BODY IRRADIATION

3. PROJECT NO.:

11. DATES AND TITLES OF PUBLICATIONS: (CONTINUED)

L. ANDREWS, G. A.: RADIATION ACCIDENTS AND THEIR MANAGEMENT. RADIATION RESEARCH, SUPPL. 7, ____, 1967.

M. LUSHBAUGH, C. C.: SOME BIOLOGICAL ENDPOINTS OF DOSIMETRIC VALUE DERIVED FROM CLINICAL DATA. IN FIRST INTERNATIONAL SYMPOSIUM ON BIOLOGICAL INTERPRETATION OF DOSE FROM ACCELERATOR PRODUCED RADIATION, E. J. VALLARIO AND ROGER WALLACE, EDITORS, UNIVERSITY OF CALIFORNIA PRESS, BERKELEY (IN PRESS), MARCH 13-16, 1967.

INTRAMURAL REPORTS

A. ANDREWS, G. A., AND LUSHBAUGH, C. C.: PRELIMINARY PROGRESS REPORT, JULY 1, 1964.

B. ANDREWS, G. A., AND LUSHBAUGH, C. C.: AEC/NASA/ORINS CONSULTATION AT DIVISION OF BIOLOGY AND MEDICINE, GERMANTOWN, APRIL 28, 1965.

C. ANDREWS, G. A., AND LUSHBAUGH, C. C.: SUPPLEMENTARY PROGRESS REPORT, JUNE 1, 1965.

D. ANDREWS, G. A., AND POLLARD, W.: CONCEPTUAL DESIGN REPORT FOR PROPOSED LOW-DOSE-RATE EXPOSURE FACILITY AT ORINS MEDICAL DIVISION COMPLEX, VANCE ROAD, OAK RIDGE, TENNESSEE, PROJECT 66-1, JULY 12, 1965.

E. LUSHBAUGH, C. C., AND BILLINGHAM, J.: WORKSHOP CONFERENCE ABOUT THE FEASIBILITY OF MEASURING RADIATION EFFECTS UPON HUMAN PERFORMANCE, JULY 22, 1965.

F. NASA WORKSHOP CONFERENCE ON SPACE RADIATION BIOLOGY, BERKELEY, CALIFORNIA, SEPTEMBER 8, 1965.

(1) LUSHBAUGH, C. C., COMAS, F., AND HOFSTRA, R.: CLINICAL STUDIES OF RADIATION EFFECTS IN MAN.

(2) ANDREWS, G. A., RADIATION ACCIDENTS AND THEIR MANAGEMENT.

G. ANDREWS, G. A., AND LUSHBAUGH, C. C.: SUMMARIZATION PROGRESS REPORT, NOVEMBER 15, 1965.

H. ANDREWS, G. A., AND LUSHBAUGH, C. C.: NASA-DIRECTORATE/OFFICE OF SPACE MEDICINE BRIEFING BOOKLET, JANUARY 22, 1966.

I. CLOUTIER, R. J., O'FOGHLUDHA, F., AND COMAS, F. V.: WORKSHOP CONFERENCE ON DOSIMETRY IN TOTAL-BODY IRRADIATION BY EXTERNAL PHOTON BEAMS, FEBRUARY 23, 1967.

J. CLOUTIER, R. J., AND BECK, J.: RADIATION SAFETY MANUAL: LOW-EXPOSURE-RATE TOTAL-BODY IRRADIATION FACILITY (LETBI), ORINS MEDICAL DIVISION, PREPARED BY ORAU RADIATION SAFETY OFFICE, JUNE 1967.

2. PROJECT TITLE: RADIOSENSITIVITY IN MAN: A STUDY OF THERAPEUTIC AND ACCIDENTAL WHOLE-BODY IRRADIATION

3. PROJECT NO.:

12. OBJECTIVE AND SCOPE:

A. THE LONG-RANGE GOAL OF THIS PROJECT IS TO ESTABLISH THE RADIOSENSITIVITY OF MAN FROM HUMAN DATA OBTAINED DURING THERAPEUTIC TRIALS AND FROM ACCIDENTAL EXPOSURES.

B. RADIOBIOLOGIC KNOWLEDGE USEFUL IN PREDICTING THE PHYSIOLOGIC OR MORPHOLOGIC RESPONSES OF MAN TO IONIZING RADIATION HAS BEEN LARGELY DERIVED FROM ANIMAL EXPERIMENTATION. ANALYSES OF HUMAN EXPOSURE DATA HAVE BEEN RELATIVELY SCARCE AND ONLY LIMITED CONFIDENCE COULD BE PLACED UPON THEIR CONJECTURES CONCERNING THE LEVELS OF RADIATION THAT WILL CAUSE DETRIMENTAL REACTIONS IN MAN. THIS PAUCITY IS MAINLY DUE TO THE DIFFICULTIES IN EVALUATING SUCH DATA BECAUSE OF NUMEROUS VARIABLES. HOWEVER, MODERN RESEARCH METHODS USING COMPUTERS WITH LARGE MEMORY STORAGE CAPACITY ARE NOW AVAILABLE FOR SUCH DATA ACCUMULATION AND EVALUATION.

C. CLINICAL DATA FROM HUMAN TOTAL-BODY IRRADIATION EXPOSURES IN THE UNITED STATES HAVE BEEN OBTAINED, EXTRACTED, AND ENCODED SO THAT THEY CAN BE ANALYZED BY MODERN MATHEMATICAL ELECTRONIC COMPUTER METHODS. THE ORINS PATIENT MATERIAL OBTAINED IN A RADIOTHERAPEUTIC PROGRAM SINCE 1957 AND ADDITIONAL HUMAN DATA (2004 CASES) OBTAINED FROM OTHER HOSPITAL CENTERS WITH SIMILAR STUDIES HAVE BEEN INCORPORATED INTO A STUDY TO DETERMINE DOSE RELATIONSHIPS IN MAN FOR ANOREXIA, NAUSEA, VOMITING, DIARRHEA, FATIGUE, WEIGHT LOSS, FEVER, ERYTHEMA, EPILATION, LYMPHOPENIA, GRANULOCYTOPENIA, ANEMIA, THROMBOCYTOPENIA, CYTOGENETIC DAMAGE, DECREASED RESISTANCE TO INFECTION, DECREASED ANTIBODY SYNTHESIS, INCREASED AGING, CARCINOGENESIS, AND LETHALITY. THE VALUES ARE BEING ASSESSED FOR DEGREE OF CLINICAL AND MATHEMATICAL CONFIDENCE TO PERMIT THEIR USE IN PREDICTING MAN'S REACTION TO THE AMBIENT RADIATIONS OF SPACE, AND TO DIRECT FURTHER CLINICAL EXPLORATION ON THE EFFECT OF IONIZING RADIATION UPON CANCEROUS AND NORMAL PROCESSES.

D. THE REASONS FOR THIS STUDY ARE MULTIFACETED. THERAPEUTIC TOTAL-BODY IRRADIATION IS EFFICACIOUS IN CONTROLLING SOME CASES OF LEUKEMIA AND LYMPHOMA AND AMELIORATING SYMPTOMS IN OTHERS. THE POSSIBILITY THAT SLOW DOSAGE RATES MAY FAVOR REPAIR OF NORMAL TISSUE AND ALLOW ITS NORMAL MITOSIS WHILE SUPPRESSING GROWTH AND REPAIR OF MALIGNANT PROCESSES HAS NOT BEEN EVALUATED IN THE PRESENT MODERN ERA OF RADIOTHERAPY AND RADIOBIOLOGY; WE PROPOSE TO TEST THIS HYPOTHESIS WITH A RADIATION FACILITY PRODUCING AN ISOTROPIC FLUX OF UNIFORM RADIATION GIVING LOW RATES OF EXPOSURE. THIS IRRADIATOR IS LARGE ENOUGH FOR PATIENTS TO LIVE IN COMFORTABLY FOR SEVERAL WEEKS. BECAUSE OF EXPANDING PROGRAMS IN NUCLEAR ENERGY AND SPACE EXPLORATION, THE NEED IS MORE ACUTE THAN EVER FOR DATA DERIVED DIRECTLY BY OBSERVATION OF MAN'S REACTION RATHER THAN ASSUMED FROM ANIMAL STUDIES. THE RETROSPECTIVE ACCUMULATION OF SUCH DATA AS ARE AVAILABLE SHOWS THAT THE DATA SUFFER FROM LACK OF MODERN DOSIMETRY, TISSUE DEPTH DOSE KNOWLEDGE, AND UNBIASED RECORDING OF SYMPTOMATOLOGY.

13. BASIS OF COST ESTIMATES:

THE COST ESTIMATES ARE BASED UPON PROGRAM EXPENSES THROUGH JUNE 30, 1967, AND PROJECTIONS THROUGH DECEMBER 31, 1969.

THE ENCODING OF ORINS 140 CHARTS WAS STARTED IN JULY OF 1964 AND REQUIRED A TOTAL OF 4 MAN-YEARS. THIS PHASE OF THE ENCODING IS COMPLETE EXCEPT FOR PATIENTS

2. PROJECT TITLE: RADIOSENSITIVITY IN MAN: A STUDY OF THERAPEUTIC AND ACCIDENTAL WHOLE-BODY IRRADIATION

3. PROJECT NO.:

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13. BASIS OF COST ESTIMATES: (CONTINUED)

CURRENTLY RECEIVING TOTAL-BODY IRRADIATION. THE EXPERIENCE GAINED IN ENCODING THE ORINS CHARTS HAS BEEN PROJECTED FOR 2004 CHARTS OBTAINED FROM OTHER HOSPITALS THROUGH JULY 1967. THE ENCODING OF THESE CHARTS WILL CONTINUE AT A LEVEL OF 7 MAN-YEARS TO COMPLETION ON DECEMBER 27, 1967. ALL TOTAL-BODY IRRADIATION CHARTS TO BE USED IN THE RETROSPECTIVE STUDIES HAVE BEEN OBTAINED FROM PARTICIPATING INSTITUTIONS AT THE END OF JUNE 1967. THE PROJECTED PERSONNEL SERVICES COST REFLECTS ALSO A RESEARCH ASSOCIATE FOR DOSIMETRY STUDIES AND A CLINICAL INVESTIGATOR.

TRAVEL EXPENSE IS BUDGETED ON THE ASSUMPTION THAT ORINS PERSONNEL WILL BE INVOLVED IN A NUMBER OF CONFERENCES, TRIPS TO CONTRIBUTING INSTITUTIONS FOR DOSIMETRY STUDIES, AND AN INCREASING USE OF CLINICAL AND PHYSIOLOGIC CONSULTANTS WITH THE DEVELOPING PROSPECTIVE STUDIES.

IN CY-1967 THE USE OF THE LOW-EXPOSURE-RATE IRRADIATOR FOR THE TREATMENT OF PATIENTS WAS BEGUN.

THE ORNL COMPUTER COSTS WILL DECREASE IF ADDITIONAL CORE CAPACITY BECOMES AVAILABLE ON THE ORAU COMPUTER. PHYSIOLOGIC MONITORING WAS OPERABLE BY MID 1967 AND BEGAN REQUIRING ON-LINE COMPUTER MONITORING CAPABILITIES. THE DATA PROCESSING COST REPRESENTS ORAU'S EFFORT IN INITIAL PROCESSING OF DATA CARDS FOR THE ORNL COMPUTER. THE ORAU IBM 1800 ON-LINE, TIME-SHARING COMPUTER COSTS WILL INCREASE SLIGHTLY ABOVE THE CY-67 COSTS AND REMAIN REASONABLY CONSTANT AT $40,000 PER YEAR.

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14. RELATIONSHIP TO OTHER PROJECTS:

FORTY-TWO U. S. MEDICAL CENTERS ARE COOPERATING IN THIS PROGRAM BY PROVIDING CLINICAL DATA FROM PREVIOUSLY TOTAL-BODY IRRADIATED PATIENTS. THE ORAU DATA PROCESSING GROUP IS PROVIDING STATISTICAL, ANALYTICAL, PROGRAMMING, CONSULTATION, AND COMPUTER SUPPORT. DOSE-RESPONSE RELATIONSHIPS DERIVED FROM THIS STUDY WERE REPORTED TO THE SPACE-RADIATION STUDY PANEL OF THE NATIONAL RESEARCH COMMITTEE OF THE NATIONAL ACADEMY OF SCIENCES, THE HARVARD WORKSHOP OF THE MANNED SPACE CRAFT CENTER, AND GODDARD SPACE FLIGHT STUDY COMMITTEE OF NASA DURING CY-67. COLLABORATION WITHIN THE MEDICAL DIVISION HAS BEEN WITH THE RADIOTHERAPY AND CLINICAL SECTIONS STUDYING MECHANISMS OF RADIATION INJURY.

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15. PROGRESS AND ACCOMPLISHMENTS IN CY-67:

DOSE-RESPONSE RELATIONSHIPS DERIVED FROM THIS STUDY FOR THE 90, 50, AND 10% PROBABILITIES OF A PATIENT RESPONDING TO WHOLE-BODY RADIATION DOSAGE WITH SYMPTOMS OF ANOREXIA, NAUSEA, VOMITING, FATIGUE, AND DIARRHEA WERE INCORPORATED INTO A BOOK (PUBLISHED IN JULY 1967), RADIOBIOLOGICAL FACTORS IN MANNED SPACE FLIGHT, EDITED BY W. H. LANGHAM AND D. GRAHN FOR THE SPACE SCIENCE BOARD OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL RESEARCH COUNCIL, TO ENABLE THEIR EARLIEST USE BY THE NATIONAL AERONAUTICS AND SPACE AGENCY IN PLANNING FOR THE APOLLO PROGRAM.

A STUDY OF THE CONCOMITANT HEMATOLOGIC EFFECTS OF RADIATION IN THESE PATIENTS WAS MADE AND REPORTED AT THE INTERNATIONAL ATOMIC ENERGY AGENCY PANEL ON THE EFFECTS OF

15. PROGRESS AND ACCOMPLISHMENTS IN CY-67: (CONTINUED)

VARIOUS TYPES OF IONIZING RADIATIONS FROM DIFFERENT SOURCES ON THE HEMATOPOIETIC TISSUES IN VIENNA, AUSTRIA.

A TWO-DAY WORKSHOP CONFERENCE HELD ON THE DOSIMETRY IN TOTAL-BODY IRRADIATION BY EXTERNAL PHOTON BEAMS, ATTENDED BY TEN INVITED PARTICIPANTS AND AN EQUAL NUMBER OF OUR STAFF, PRODUCED A UNANIMITY OF OPINION THAT RADIATION EXPOSURE CANNOT BE USED TO INDICATE THE DOSE; THAT THE DOSE (IN RADS) TO THE CRITICAL ORGAN OR VOLUME OF THE BODY IS THE IDEAL MEASUREMENT TO USE IN RELATING THE DEGREE OF PHYSIOLOGIC OR PATHOLOGIC RESPONSE; AND THAT WHERE THE TRIGGER SITE FOR ELICITING RADIATION-INDUCED REACTIONS IS UNKNOWN, THE BEST DOSE EXPRESSION IS THE AVERAGE WHOLE-BODY DOSE. UNIVERSAL USE OF SUCH DOSAGE EXPRESSIONS WOULD SIMPLIFY ALL FUTURE RETROSPECTIVE STUDIES BY ALLOWING ANY INVESTIGATOR TO REESTIMATE THE DOSE TO ANY BODY COMPARTMENT (SUCH AS TOTAL SKIN, FOR EXAMPLE).

THE 163 CLINICAL CASE STUDIES USED AS THE BASIS FOR THIS STUDY WERE MERGED WITH APPROXIMATELY 800 ADDITIONAL OBSERVATIONAL REPORTS OF SINGLE WHOLE-BODY RADIATION EXPOSURES IN MAN FROM THE USA (SEE APPENDED AUDIT). IN ADDITION, 216 CASE STUDIES WHERE RADIATION EXPOSURE WAS MADE OVER GREATER TIME PERIODS THAN ONE DAY BUT LESS THAN EIGHT DAYS WERE OBTAINED AND ENCODED INTO THE SYSTEM. IN ADDITION, ALMOST 650 CASE STUDIES OF FRACTIONATED RADIATION EXPOSURES PROTRACTED BEYOND EIGHT DAYS TO AS LONG AS THREE YEARS WERE OBTAINED. THE DATA ARE BEING EXTRACTED AND ENCODED FOR INTEGRATION WITHIN THE DATA MANAGEMENT SYSTEM FOR LATER ANALYSIS.

FINDING A COMMON RADIATION-DOSE DENOMINATOR FOR THE LARGEST POSSIBLE NUMBER OF THESE EXPOSURES WAS THE MAJOR TASK OF PART OF THE GROUP AS IT IS THE MOST IMPORTANT SINGLE DISCRIMINATIVE REQUIREMENT FOR SUCH DOSE-RESPONSE STUDIES. A SYSTEM ULTIMATELY PROGRAMMED FOR AUTOMATIC COMPUTATION WAS DEVELOPED USING MAYNEORD'S FORMULA TO ESTIMATE THE WHOLE-BODY AVERAGE DOSE CORRECTED FOR THE PATIENT'S BODY WEIGHT AND HEIGHT. A PARALLEL SEARCH WAS ALSO MADE FOR STATISTICAL SYSTEMS FOR DETERMINING DOSE-RESPONSE RELATIONS AND MAKING EXTRAPOLATED PREDICTIONS TO LOW DOSAGES THAT HAVE SOME PROBABILITY FOR OCCURRING DURING SPACE EXPLORATION. AN ANALYTICAL METHOD WAS USED IN PARALLEL WITH PROBIT ANALYSIS TO EXPAND OUR STUDY TO INCLUDE ABOUT 300 SINGLE EXPOSURES OF PATIENTS. STRICT CRITERIA REQUIRED FOR MACHINE OPERATED DATA COLLATION FROM THE CLINICAL RECORDS PREVENTED USE OF 500 OTHER CASES BECAUSE OF INADEQUATELY RECORDED MEDICAL AND NURSING NOTES.

TO DETERMINE IF THE WHOLE-BODY MUST BE IRRADIATED WITH A GREATER OR LESSER DOSE THAN A SINGLE AREA OF THE BODY, ANOTHER STUDY OF FRACTIONATED PORTAL IRRADIATION OF THE TORSO WAS BEGUN. THIS STUDY WILL COMPRISE 227 PATIENTS WITH 413 SERIES OF THERAPEUTIC EXPOSURES OF 2-10 PORTAL IRRADIATIONS OVER ABOUT 10 DAYS.

ANOTHER MAJOR ACCOMPLISHMENT BASIC TO THESE STUDIES WAS THE DEVELOPMENT OF AN EFFICIENT DATA MANAGEMENT SYSTEM AND DATA BANK. A PROGRAM LIBRARY OF SUBROUTINES WAS DEVELOPED TO MEASURE INCIDENCES OF CERTAIN RESPONSES EITHER QUALITATIVELY OR QUANTITATIVELY OVER PRESCRIBED POST-IRRADIATION TIME SEGMENTS. ADDITIONAL PROGRAMS FOR MATHEMATICAL AND STATISTICAL ANALYSIS AND DATA PLOTTING WERE WRITTEN OR MODIFIED TO OPERATE WITHIN OUR PROGRAM REQUIREMENTS.

THE LOW-EXPOSURE-RATE TOTAL-BODY FACILITY WAS CONSTRUCTED AND BY CY-67 WAS 95% COMPLETE. A PHYSIOLOGIC MONITORING SYSTEM FOR THIS FACILITY AND THE OLDER MEDIUM-LEVEL EXPOSURE FACILITY WAS DESIGNED AND PURCHASED.

2. Project Title: Radiosensitivity in Man: A Study of Therapeutic and Accidental Whole-Body Irradiation

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15. Progress and Accomplishments in CY-67: (continued)

The retrospective study of single radiation dose effects in patients previously treated with total-body irradiation for malignant disease was completed and being written up in detail by midyear. Approximately 900 case histories were involved in this analytical study. To complete this study no old case histories of single exposures were collected from the field after June 1967, but new therapeutic observations within the recent past and present years were obtained. In addition, the first six months of the calendar year were devoted to finishing up the collection of U. S. and Canadian experience with fractionated total-body radiation exposures in patients. This material was encoded concurrently with its collection so that its incorporation into the data bank could be completed as early in CY-68 as possible. In the latter half of CY-67 we are focusing on comparing the effects of fractionated portal and fractional total-body irradiation with single dose therapy in order to produce objective evidence for the existence of radiation repair mechanisms in man. Our principal objective was to determine whether a dose divided into smaller fractions over various time periods was better tolerated physiologically by the patient and whether such fractionation did or did not produce comparable degrees of hematologic system depression.

Operation of this facility depended in large measure upon completion of the isodose study that determined the spatial variation in the radiation flux within the (inner) therapeutic exposure room, and the isodose (depth dose) patterns within man-like plastic phantoms. This study required the development of a dosimetry system that measures the integrated and local exposures of the patient so that accurate estimates of the doses to various organs and tissues can be made. This study, to be completed in late CY-67, involves the use of air and tissue-equivalent ionization chambers, and their associated electrometers; an IBM 1800 on-line computer to monitor exposure patterns over time and report on the functioning of the ten cobalt-60 radiation sources and their regulatory and safety interlocks, and a retrospectively analyzed dosimetry system using multiple film badges, and thermoluminescent powder and glass rod dosimeters that are placed on various parts of the patient's body and at selected sites in the irradiation room. Computer programs were developed that: (1) increased the speed and accuracy of the analysis of the dosimetry measurements, and (2) enabled routine analysis of such physiologic signals from the patient being irradiated as the EKG, cardiac and pulmonary rate variance, and pulmonary impedance wave forms. These analytic programs enabled a search to be made for subconscious levels of physiologic dysfunction in the absence of other objective signs of radiation sickness.

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16. Program Plans for CY-68:

The main objectives in CY-68 will be threefold: (1) completion of the retrospective study of human dose-response relations to various patterns of fractionated total-body irradiation, (2) completion of the retrospective study of the comparative incidence of deleterious physiologic responses when such fractionated exposures are made to restricted portions of the body instead of the total body; and (3) a steady growth in the on-going phase of this study to determine, by using the new low exposure total-body irradiation facility and its physiologic monitoring system,

16. Program Plans for CY-68: (continued)

the tolerance of man to withstand radiation exposure rates of less than 2 R per hour for varying lengths of time. A comparison of the dose relations for the various physiologic and laboratory endpoints observed in radiation sickness and the hematologic syndrome will be made between: (1) single and fractionated total-body irradiation, (2) single TBI and fractionated partial body exposures, and (3) fractionated total-body and fractionated partial-body exposures. The results of these comparative studies should enable us to detect any deviations that occur from the expected response patterns in patients being treated with the low-exposure rate of the new irradiation facility.

Concurrently the computer data bank of human total-body irradiation exposures from therapeutic studies and radiation accidents will be kept up to date, condensed wherever possible, and utilized for searching for any evidence in support of any new observations or theories made as a result of the progressive therapeutic irradiation studies.

The medium-exposure-rate total-body (cesium-137) irradiator (METBI), used in the single dose (1.5 R/hr) total-body study from the ORAU Medical Division will continue to be used in the radiotherapy of chronic lymphatic leukemia, lymphoma, polycythemia, involving various stem cells, and chronic granulocytic leukemia. A telemetering physiologic monitoring system will be developed to overcome the physical distance between this irradiator (METBI) and the on-line data collection and analysis facility using the IBM 1800 computer housed in the new low-exposure irradiation facility (LETBI). A comparison will be made of the physiological signals from patients suffering radiation sickness in the METBI (where the retrospective study has defined the expected incidence of anorexia, nausea, and vomiting over the 25 to 200 R exposure range) with signals from patients undergoing protracted low-exposure-rate irradiation in the new (LETBI) facility. It is anticipated that such a comparison will underscore the diminution in the incidence and severity of acute radiation sickness expected with low dose rates. Since the first three persons treated in the new facility failed to produce clinical or electronically detectable signs of acute radiation sickness, we will attempt to increase our detector sensitivity by incorporating electonic skin galvanic response and gastric pressure and acidity ("endoradiosone") monitoring devices in the present physiologic monitoring system. The evaluation of these as well as the other electronically obtained physiologically produced signals will require physiologic monitoring of unirradiated patients showing clinical signs and symptoms of nausea, vomiting, diarrhea, fever, and cardiac and pulmonary abnormalities. Full development of this program will require our obtaining a physiologically and electronically oriented clinician on the clinical investigation staff.

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17. Program Plans for CY-69:

Present experience with the low-exposure rate facility indicates that about 30 therapeutic studies will have been completed during CY-67 and CY-68. The exposure periods in these trials now are planned to extend over 3 to 5 days producing an exposure of about 100 to 150 R (average whole-body dose of 66 to 100 rads). Concurrent evaluation of the effectiveness of such therapy in comparison with the higher dose rate facility and the fractionated total-body exposures now being carried out

2. PROJECT TITLE: RADIOSENSITIVITY IN MAN: A STUDY OF THERAPEUTIC AND ACCIDENTAL WHOLE-BODY IRRADIATION

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17. PROGRAM PLANS FOR CY-69: (CONTINUED)

AT NIH CLINICAL CENTERS WILL BE MADE. OTHER TEMPORAL PATTERNS OF RADIATION EXPOSURE ARE SCHEDULED TO EVALUATE BOTH CLINICAL EFFECTIVENESS AND MORE EFFICIENT UTILIZATION OF THE FACILITY. FOR EXAMPLE, SOME RECENT STUDIES (NIH) SUGGEST THAT 10 R TBI EXPOSURES THREE TIMES WEEKLY FOR SEVERAL WEEKS FOLLOWED BY 10 R TOTAL-BODY EXPOSURES FOR ONE DAY, ONCE A MONTH, PRODUCES AND MAINTAINS AMELIORATION OF SYMPTOMS AS LONG AS A YEAR OR MORE IN PERSONS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND LYMPHOSARCOMA. A COMPARATIVE STUDY USING THE 1.5 R/MIN FACILITY AND THE 1.5 R/ HR FACILITY TO TREAT PATIENTS WITH SUCH DOSAGE SCHEDULES WOULD BE MOST MEANINGFUL TOWARD UNDERSTANDING VARIATION IN TOTAL-BODY AND SPECIFIC ORGAN RADIOSENSITIVITY. SIMULTANEOUSLY, A GREATER NUMBER OF PATIENTS COULD BE STUDIED THERAPEUTICALLY AND MORE PROGRESS MADE TOWARD DETERMINING THE OPTIMUM EXPOSURE CONDITIONS, AS WELL AS THE LIMITATIONS, OF TOTAL-BODY RADIOTHERAPY OF THESE DISEASES.

18. SIGNIFICANT CAPITAL EQUIPMENT AND CONSTRUCTION REQUIREMENTS:

	CY-68	CY-69
TELEMETERING SYSTEM	$12,000	
ENDORADIOSONE DEVICE	5,000	
SKIN GALVANIC RESPONSE SYSTEM	3,000	
MISCELLANEOUS	8,000	
COMPUTER COMMUNICATION AND DISPLAY DEVICES		$20,000

APPENDIX
CASE ORIGIN AND COMPOSITION
RETROSPECTIVE AEC/NASA STUDY OF HUMAN TOTAL-BODY IRRADIATION EFFECTS

Hospital Providing Study	Therapy Exposures	Coded	Exposure Class*		
			<D	~1W	>W
Albert Einstein Medical Center	1	1	1		
Baylor U.: Jefferson Davis Hospital	71	71	48	4	19
V. A. Hospital at Houston	36	36	18	8	10
Texas Medical Center	4	4	1	3	
Burge Protestant Hospital	5	5	1	2	2
Cincinnati General	32	32	29	1	2
City of Hope Medical Center	58	58	36	8	14
Charity Hospital	100	54	4	18	78
Colorado General	1	1			1
Ellis Fischel State Cancer Center	84	84	2	9	73
Franklin Hospital	56				56
Jefferson Medical College	11	11	11		
Long Beach Community Hospital	1	1	1		
Los Alamos Hospital	9	9	9		
Mary Imogene Bassett	27	27	15	11	1
Massachusetts General (McG) (LR)	207	7	7		200
M. D. Anderson	279	279	272	1	6
Medical College of Virginia	5	5	5		
New York Memorial (CH) (N)	236	236	35	118	83
ORINS	140	139	135	2	3
Penrose Cancer Clinic	73	73	1	5	67
Peter Bent Brigham	11	11	2	8	1
Portland: Emanuel Hospital	54	54	49		5
Dr. Hyman's Clinic	49	49	26		23
Portland Medical Center	33	33	2	19	12
Providence Hospital	288	288	236	3	49
Rhode Island Accident	1	1	1		
Spokane: Deaconess Hospital	6				6
Rockwood Clinic	7				7
Sacred Heart Hospital	6				6
Milo Harris Clinic	15				15
Swedish Hospital	28				28
Temple University	29	29	15	5	9
Thomas M. Fitzgerald Mercy	4	4	4		
Toronto, Ontario, Canada	26		14		12
U. S. Naval Hospital	11	11	7		4
U. of California Medical School, S. F.	169				169
U. of Michigan	312	281	2	50	260
U. of Washington	3	3	2	1	
V. A. Hospital at Denver	25	25	2		23
V. A. Hospital at Long Beach	2	2	2		
V. A. Hospital at New Orleans	57	57	5	16	36
Vancouver: British Columbia Cancer Inst.	15				15
Royal Columbian	3				3
Vancouver General	8				8
White Memorial Medical Center	2	2	2		
TOTALS	2,600	1,983	1,002	292	1,306

* <D = less than one day exposure
~1W = less than one week exposure
>W = greater than one week exposure

UNITED STATES
ATOMIC ENERGY COMMISSION
OAK RIDGE OPERATIONS
P O BOX E
OAK RIDGE, TENNESSEE 37830

October 23, 1969

John R. Totter, Director, Division of Biology and Medicine, HQ

ORAU STUDY OF THERAPEUTIC AND ACCIDENTAL WHOLE BODY IRRADIATION FOR NASA (ORDER W-12,792, TASK 9, INTERAGENCY AGREEMENT 40-35-64)

The enclosed program proposal (Schedule 189) has been submitted by ORAU to describe the scope of work and estimated cost proposed for continuation during CY 1970 of the studies for NASA having the long range objective of establishing the radiosensitivity of man from human data obtained during therapeutic trials and from accidental exposure. (The proposal also includes program and budget plans for CY 1971 for NASA advance planning.)

The studies, initiated in June 1964, have continued in succeeding calendar years, and are currently proceeding under Amendment No. 5 to NASA Order W-12,792, Task 9. Through Amendment No. 5, which provided funds in the amount of $270,000 during CY 1969, NASA has funded a total of $1,420,000 for these studies.

Continuing progress made in CY 1969 toward the long range goal stated above, the proposed effort during CY 1970 anticipates (1) completion of a detailed report summarizing the findings of the retrospective study of human hemotologic and gastrointestinal responses from past therapeutic trials throughout the USA; (2) continuation of "prospective" human radiation sensitivity studies with observations obtained through utilization of the low and medium total body irradiation facilities and physiologic monitoring systems available at ORAU; and (3) the development of dosimetry systems for the measurement of non-uniform radiation exposure and the application of dose reduction factors proper to each radiation experience.

The proposed studies are estimated to require NASA support for an operating cost level of $240,000 in CY 1970. Based on the cost experience through June 1969, and the estimated probable fund requirements through December 1969, it appears at this time that there will be approximately $60,000 in unexpended NASA funds available to be applied to the next period of performance. The new NASA funding therefore required for the proposed program totaling $240,000 would be $180,000.

We believe the ORAU proposal is in accordance with AEC and NASA program plans and recommend your submission of the proposal to NASA for approval and issuance of appropriate documentation authorizing continuation of the ORAU studies in CY 1970.

Herman M. Roth

Herman M. Roth, Director
Laboratory and University Division
Oak Ridge Operations

OL:MJR

Enclosure:
ORAU Proposal (6)

cc w/encl:
S. G. English, HQ
R. C. Armstrong
C. W. Hill (2)
N. A. Shearon

SCHEDULE 189

EXPLANATION FOR OPERATING COSTS

Oak Ridge Operations	40 04
Field Office or Laboratory	Budget Activity No.

1A.	Contractor: Oak Ridge Associated Universities, Inc.	1B.	Contract No.: AT-(40-1)-GEN-33
2.	Project Title: Radiosensitivity in Man: A Study of Therapeutic and Accidental Whole-Body Irradiation NASA	3.	Project No.:
4.	Starting Date of Project: Continuing	5.	Date Schedule Prepared: October 8, 1969
6.	Method of Reporting: Annually	7.	Working Location: Oak Ridge, Tennessee
8A.	Person in Charge: G. A. Andrews Ralph M. Kniseley	8B.	Principal Investigator: G. A. Andrews, C. C. Lushbaugh, R. M. Kniseley, C. L. Edwards, and F. Comas

9. Man Years:	Funded CY-1969	Estimated CY-1970	Estimated CY-1971
	12.0*	13.0	13.0

10. Funding and Costs:	Estimated CY-1969	Estimated CY-1970	Estimated CY-1971
Funding			
Prior Year Unexpended Funds	$ 21,000	$ 60,000	$ 0
Current Year Funding	270,000	180,000	220,000
Total Funds Available	$291,000	$240,000	$220,000
Costs			
Personal Services	$116,000	$122,000	$128,000
Travel	4,300	2,000	2,000
Materials & Supplies	4,900	6,000	5,000
Computer Services	6,000	8,000	5,000
ORAU - IBM	11,000	20,000	8,000
Equipment	26,500	20,000	15,000
Technical Services	4,800	9,000	8,000
Overhead	57,500	53,000	49,000
Total Costs	$231,000	$240,000	$220,000

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* Dr. Ricks, a physiologist, was employed September 1, 1969.

2. Project Title: Radiosensitivity in Man: A Study of Therapeutic and Accidental Whole-Body Irradiation

3. Project No.:

1. Dates and Titles of Publications:

Open Literature Reports from this and Related AEC Projects:

A. Lushbaugh, C.C., Hofstra, R., Roth, R.E., and Andrews, G.A.: ED_{50} for gastrointestinal responses in man. Radiation Research 25, 114, May 1965 (abstract).

B. Andrews, G.A., Auxier, J.A., and Lushbaugh, C.C.: The importance of dosimetry to the medical management of persons accidentally exposed to high levels of radiation. In Personnel Dosimetry for Radiation Accidents, IAEA, Vienna, August 1965.

C. Lushbaugh, C.C., Comas, F., Saenger, E.L., Jacobs, M.: Radiosensitivity of man by extrapolation from studies of total-body irradiation of patients (invited lecture, February 15, 1966). Radiation Research 27, 487-488, March 1966.

D. Andrews, G.A.: Treatment of radiation injury. J. Mississippi Med. Assoc. 7, 534-538, 1966.

E. Andrews, G.A., Lushbaugh, C.C., and Kniseley, R.M.: Proceedings of a Panel on Effects of Total-Body Irradiation in the Human Being. IAEA, Vienna, May 17, 1966.

F. Dalton, C.P., and Cloutier, R.J.: An arrangement of radioactive sources for a low-exposure-rate total-body irradiation facility. Physics in Medicine and Biology 12, 116, 1967.

G. Dalton, C.P., and Cloutier, R.J.: Source arrangement for a low-exposure-rate total-body irradiation facility for man. USAEC Report ORINS-52, May 1, 1967, 205 pages.

H. Fanger, H., and Lushbaugh, C.C.: Radiation death from cardiovascular shock following a criticality accident: Report of a second death from a newly defined human radiation death syndrome. Arch. Path. 83, 446-460, May 1967.

I. Lushbaugh, C.C.: Editorial, Radiation and Shock, JAMA 200, 181, 1967.

J. Langham, W., editor: Space Radiation Study Panel: Radiobiologic Factors in Manned Space Flight. July 1, 1967.

(1) Lushbaugh, C.C., Andrews, G.A., and Langham, W.: Prodromal response, p. 76-90.

(2) Conard, R., Andrews, G.A., and Langham, W.: Hematologic effects, p. 90-105.

(3) Langham, W., and Lushbaugh, C.C.: Early lethality, p. 105-124.

(4) Thompson, J., and Andrews, G.A.: Chemical and biological protection, p. 218-230.

2. Project Title: Radiosensitivity in Man: A Study of Therapeutic and Accidental Whole-Body Irradiation

3. Project No.:

. Dates and Titles of Publications: (continued)

K. Lushbaugh, C.C., Comas, F., and Hofstra, R.: Clinical studies of radiation effects in man: A preliminary report of a retrospective search for dose-response relationships in the prodromal syndrome. Radiation Research Suppl. 7, 398-412, November 1967.

L. Andrews, G.A.: Radiation accidents and their management. Radiation Research Suppl. 7, 390-397, November 1967.

M. Lushbaugh, C.C.: Some biological endpoints of dosimetric value derived from clinical data. In First International Symposium on Biological Interpretation of Dose from Accelerator Produced Radiation, March 13-16, 1967, E. J. Vallario, editor. DTIE CONF-670305.

N. Lushbaugh, C.C.: Recent progress in assessment of human resistance to total-body irradiation. In Proceedings of a Symposium Postattack Recovery from Nuclear War, held at Fort Monroe, Virginia, November 6-9, 1967.

O. Lushbaugh, C.C., Comas, F., Edwards, C.L., and Andrews, G.A.: Clinical evidence of dose-rate effects in total-body irradiation in man. In The Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology, held April 29-May 1, 1968, Oak Ridge, Tennessee, CONF-680410.

P. Beck, W.L., Callis, E.L., and Cloutier, R.J.: Phantom depth-dose measurements with extruded LiF in a low-exposure-rate total-body irradiator. In Proceedings of the Second International Conference on Luminescence Dosimetry, September 23-26, 1968, USAEC Report CONF-680920, 1968, pp. 976-989.

Q. Comas, F.V.: The time factor in fractionated irradiation of mouse skin. In The Proceedings of a Symposium on Dose Rate in Mammalian Radiation Biology, held April 29-My 1, 1968, Oak Ridge, Tennessee, USAEC Report, CONF-680410, 1968, pp. 18.1-18.12.

R. Comas, F.V., Andrews, G.A., and Nelson, B.: Spleen irradiation in secondary hypersplenism. Amer. J. Roentgenol. 104, 668-673, 1968.

S. Lushbaugh, C.C., Comas, F.V., and Andrews, G.A.: Radiation dose-response relations derived from clinical data, Health Physics 15(2), 165-166, 1968 (abstract).

T. Bond, V.P., Osborne, J.W., Lesher, S., Lushbaugh, C.C., and Hornsey, S.: Panel discussion on mechanism of intestinal radiation death. In Gastrointestinal Radiation Injury, Report of a symposium held at Richland, Washington, September 25-28, 1966. Exerpta Medica, March 1968, pp. 352-373.

U. Ur, A., and Lushbaugh, C.C.. Some effects of electrical fields on red blood cells and electronic red blood cell sizing. Brit. J. Haemat. 15, 527-538, 1968.

2. Project Title: Radiosensitivity in Man: A Study of Therapeutic and Accidental Whole-Body Irradiation

3. Project No.:

.. Dates and Titles of Publications: (continued)

V. Andrews, G.A.: The therapeutic use of bone-marrow transplantation. In Proceedings of the International Conference on Leukemia-Lymphoma, Ann Arbor, 1967, edited by Chris J. D. Zarofonetis, Philadelphia, Lea and Febiger, 1968, pp. 423-432.

W. Andrews, G.A., Kniseley, R.M., Vodopick, Helen, Bergner, P.E-E., and Lushbaugh, C.C.: Hematologic responses to total-body irradiation, presented at Gesellschaft Fur Nuclearmedizin, Wiesbaden, Germany, September 28, 1968 (in press).

X. Lushbaugh, C.C.: Theoretical and practical aspects of models explaining "gastrointestinal death" and other lethal radiation syndromes. In Report of US/Japanese Symposium on Comparative Cellular and Species Radiosensitivity held in Kyoto, Japan, May 20-23, 1968, edited by V. P. Bond, M.D., and Tsutomu Sugahara, M.D., Igaku Shoin Ltd., Tokyo, Japan, March 1969, pp. 288-297.

Y. Lushbaugh, C.C., Frome, E.L., Davis, H.T., and Bibler, D.S.: The power spectrum of the impedance pneumograph: A data reduction system producing an analytical parameter of potential clinical usefulness. Aerospace Medicine 40, 425-429, 1969.

Z. Upton, A.C., and Lushbaugh, C.C.: The pathological anatomy of .al-body irradiation. In Atomic Medicine, 5th edition, Charles F. Behrens and E. Richard King, editors, Williams and Wilkins Co. (in press).

AA. Morris, A.C., Jr., Barclay, T.R., and Lushbaugh, C.C.: Monitoring physiologic responses during total-body irradiation therapy. Second International Conference on Medical Physics, August 11-15, 1969, Boston, Mass. (abstract).

BB. Beck, William L., Cloutier, R.J., Comas, F.V., and Lushbaugh, C.C.: Human depth-dose estimates in multidirectional gamma-ray fields, Second International Conference on Medical Physics, August 11-15, 1969, Boston, Mass. (abstract).

CC. Lushbaugh, C.C., and Auxier, John: Reestimation of human LD_{50} radiation levels at Hiroshima and Nagasaki. Radiation Research 39, 526, 1969 (abstract).

DD. Upton, A.C., Cosgrove, G.E., and Lushbaugh, C.C.: The induction of glandular carcinoma of the stomach in mice by whole-body irradiation. US-Japan Conference on Experimental Carcinoma of the Glandular Stomach, held at Hakone, Japan on June 10-13, 1969 (in press).

EE. Lushbaugh, C.C.: Reflections on some recent progress in human radiobiology. In Advances in Radiation Biology, Vol. 3, edited by L. G. Augenstein, R. Mason, and M. Zelle, pp. 277-314, 1969.

2. Project Title: Radiosensitivity in Man:
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. Dates and Titles of Publications: (continued)

Intramural Reports

A. Andrews, G.A., and Lushbaugh, C.C.: Preliminary Progress Report, July 1, 1964.

B. Andrews, G.A., and Lushbaugh, C.C.: AEC/NASA/ORINS Consultation at Division of Biology and Medicine, Germantown, April 28, 1965.

C. Andrews, G.A., and Lushbaugh, C.C.: Supplementary Progress Report, June 1, 1965.

D. Andrews, G.A., and Pollard, W.: Conceptual design report for proposed low-dose-rate exposure facility at ORINS Medical Division Complex, Vance Road, Oak Ridge, Tennessee, Project 66-1, July 12, 1965.

E. Lushbaugh, C.C., and Billingham, J.: Workshop Conference about the Feasibility of Measuring Radiation Effects upon Human Performance, July 22, 1965.

F. NASA Workshop Conference on Space Radiation Biology, Berkeley, California, September 8, 1965.

(1) Lushbaugh, C.C., Comas, F., and Hofstra, R.: Clinical studies of radiation effects in man.

(2) Andrews, G.A.: Radiation accidents and their management.

G. Andrews, G.A., and Lushbaugh, C.C.: Summarization Progress Report, November 15, 1965.

H. Andrews, G.A., and Lushbaugh, C.C.: NASA-Directorate/Office of Space Medicine Briefing Booklet, January 22, 1966.

I. Cloutier, R.J., O'Foghludha, F., and Comas, F.V.: Workshop Conference on Dosimetry in Total-Body Irradiation by External Photon Beams, February 23, 1967.

J. Cloutier, R.J., and Beck, J.: Radiation Safety Manual: Low-exposure-rate total-body irradiation facility (LETBI), ORINS Medical Division, prepared by ORAU Radiation Safety Office, June 1967.

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12. Objective and Scope:

The long-range goal of this project is to refine our knowledge of the radiosensitivity of man from human data obtained from therapeutic trials and accidental exposures. Knowledge of human radiobiology is scarce and more is needed to predict the physiologic or morphologic responses of man to ionizing

2. Project Title: Radiosensitivity in Man:
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. Objective and Scope: (continued)

radiation. Up to now such predictions have been largely derived from animal experimentation. Confidence is limited on previous conjectures concerning the levels of radiation that will cause detrimental human reactions. The inherent difficulties in evaluating voluminous clinical data containing numerous variables however have now been largely overcome. Modern research methods using computers with large memory storage capacity have enabled us to construct a human radiation-injury data bank containing clinical data from more than 3000 human total-body irradiation exposures in the United States. These charts have been extracted, and encoded and are being analyzed by modern mathematical electronic computer methods. The ORAU patient studies obtained in a radiotherapeutic program since 1957, and additional human data (~3000 cases) obtained from other hospital centers with similar studies have been incorporated into a study to determine dose relationships in man for anorexia, nausea, vomiting, diarrhea, fatigue, weight loss, fever, erythema, epilation, lymphopenia, granulocytopenia, anemia, thrombocytopenia, cytogenetic damage, decreased resistance to infection, decreased antibody synthesis, increased aging and carcinogenesis. The values are being assessed for degree of clinical and mathematical confidence to permit their use in predicting man's reaction to the ambient radiations of space, and to direct further clinical exploration on the effect of ionizing radiation upon cancerous and normal processes.

There are multiple reasons for this study overall. Therapeutic total-body irradiation is efficacious in controlling some cases of leukemia and lymphoma and ameliorating symptoms in others. The possibility that low dose rates may favor repair of normal tissue in contrast to malignant processes has not been evaluated in the present modern era of radiotherapy and radiobiology; we propose to test this hypothesis with a radiation facility producing an isotropic flux of uniform radiation giving low rates of exposure. This irradiator is large enough for patients to live in comfortably for several weeks. Because of expanding programs in nuclear energy and space exploration, the need is more acute than ever for data derived directly by observation of man's reaction rather than assumed from animal studies. The retrospective accumulation of such data as are available shows that the old data suffer from lack of modern dosimetry, tissue depth dose knowledge, biased recording of symptomatology, and incomplete and inaccurate records.

Recent progress (CY-69, see paragraphs 15) has helped define our objectives better in relation to the needs of the manned space program for human radiobiologic knowledge. Apollo 10 and 11 flights showed that moon exploration can be accomplished without any significant radiation exposure if the sun is silent. Randomly occurring solar flares can, however, produce exposure fields of variable dose rates that could result in combinations of protracted low and pulsed (fractionated) high dose rate exposures. How rapidly these dose fractions can be repaired by man to keep them from summing into an effective damaging dose is the most pertinent question yet to be answered. Our results this year reveal some of the constraining limits for chronic radiation of man (patients) and suggest further lines of research on this problem.

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13. Basis of Cost Estimates:

The cost estimates are based upon program expenses through September 1969, and projections through December 31, 1971.

The encoding of ORAU Medical Division's 140 charts was started in July 1964, and required a total of four man years. The encoding of the clinical experience of ORAU Medical Division is now complete including patients currently receiving total-body irradiation. Twenty new TBI therapeutic studies have been completed in the new low-dose-rate irradiation facility and 10 others have been done in parallel in the METBI. Three of these have been fractionated for five days a week. The experience gained in encoding the ORAU charts was used for building the data bank containing the information in 3108 charts obtained from other hospitals. The actual encoding of these charts in digital form was completed by March 1968. Storing and editing the data so that it is contained in a retrievable taped data bank from which specific answers to complicated mathematical queries can be obtained, required an additional year of data processing, programming, and systems construction and was completed this year. High costs of graphing for visual appraisal and mathematical data reduction of hematologic and clinical data of these chronically irradiated persons have been avoided by installation of a roller-type programmable plotter in line with the IBM-1800 computer. The purchase of the IBM-1800 by USAEC for Medical Division use in this and other projects greatly reduced our anticipated computer useage and rental costs. The concurrent use of the medium-exposure-rate TBI facility (METBI) and the low-exposure-rate (LETBI) facility have required our developing a second physiologic monitoring (portable) station that cost about twice the estimated cost of $12,000 in the CY-69 budget. Our search for a staff physiologist to help use and interpret these monitoring instruments with our irradiated patients was successful in 1969. He should enable us to expand the system to include studies using the endoradiosone and galvanic response systems for detecting the earliest signs of radiation-induced gastrointestinal distress. The proposed use of these systems has been approved and budgeted previously but lack of a staff member in this field of research prevented our making these studies. In addition to the physiologist, we in 1969 improved our technical staff support for prospective studies of patients undergoing protracted and fractionated irradiation by obtaining the part-time services of a hematologic and biomedical technician and a full time research assistant in radiobiology. Thus the increased personnel service costs reflect the change over from encoding of large volumes of old clinical data and its evaluation to actual live studies of patients undergoing radiotherapy with TBI at medium (METBI) and slow dose rates (LETBI); the relatively low salaries of many encoding clerks being offset by our need for more highly skilled technical personnel.

Travel expense is budgeted on the assumption that ORAU staff personnel working on the NASA project will need to be involved in pertinent radiobiologic conferences, trips to contributing institutions for dosimetry studies, and to collaborating government agencies who have mutual interests in protecting man from radiation hazards.

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. Basis of Cost Estimates: (continued)

We projected for CY-70 a decrease in the ORNL computer costs if additional core capacity became available on the ORAU computer. This was finally obtained, and thus many involved statistical analyses can now be done at ORAU. In addition, our efforts to develop real-time programs that will analyze a patient' progress under protracted radiation exposure (4 to 8 days long) require this project having available to it a greater proportion of the IBM-1800 on-line, time-sharing computer. Providing that programming personnel and statisticians continue to be available to us for this project, our projected costs for computer services are decreased from those stated in our supplementary schedule 189, July 1968. Thus our projections for computer costs for CY-70 reflect the growth of the AEC owned ORAU IBM-1800 system so that these costs are stabilized and decreased by taking over locally an increasingly larger proportion of work load from the remote ORNL computing center.

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14. Relationship to Other Projects:

Forty-two US medical centers have cooperated in this program by providing clinical data from patients previously treated with total-body irradiation. Many of the physicians and radiation physicists who participated in these therapeutic studies originally continue to collaborate with us as our study develops. Dose-response relations derived from these data are reported to the Space Radiation Study Panel of the National Research Council of the National Academy of Sciences. This active committee, to which Dr. Lushbaugh belongs, incorporated our findings in their report: Radiobiological Factors in Manned Space Flight, published July 1967. Our data have also been used in the Harvard Workshop Conference of Manned Space Craft Center and the Goddard Space Flight Study Committee, Boston, 1967; the NASA Workshop Conference and program review of NASA supported radiobiologic programs, Berkeley, 1967; the University of Tennessee/Atomic Energy Commission symposium on Dose Rate in Mammalian Radiation Biology, Oak Ridge, April 1968; and the Plenary Session of the Annual Health Physics meeting that concerned man's radiosensitivity, Denver, June 1968; Special Committee #14 of the National Council on Radiation Protection and Measurements; and the Advisory Committee of the National Plutonium Registry.

In addition, under the direction of Col. John Pickering, NASA Headquarters, and Dr. C. Barnes, NASA at Houston, collaboration and mutual data exchange - communication routes have been established between our project and those of Dr. Edward Moseley, Neurophysiology, and Dr. Craig Fischer, Lunar Receiving Laboratory, NASA Manned Space Craft Center, Houston.

Within the Medical Division, our project has strong cross ties with and is helped by the clinical personnel of the radiotherapy and clinical investigation sections who are studying mechanism of radiation injury under ORAU's AEC Contract AT-(40-1)GEN-33. No charges are made for the clinical staff's support of the LETBI and METBI studies in which the patients require extensive medical and nursing care on a 24-hour basis for periods of time

Relationship to Other Projects: (continued)

up to 42 days. In addition, a mutually cooperative study has been arranged without additional cost to NASA for determining what levels of single, repeated, or protracted irradiation exposures result in alteration of the bacteriologic flora of the persons exposed. This study has received its main financial support from the Army but is also supported by the AEC budget. The AEC contractural support constructed for the Medical Division's use a laminar air-flow sterile, 2-bed hospital ward for the care of persons without adequate bone marrow production of blood cells as after total-body irradiation or other bone marrow injury.

15. Progress in CY-69:

The completion of the taped data bank of human radiation exposures early in 1969 has enabled us to concentrate on finishing the last part of the retrospective study of human radiation exposures. Previously we completed the study of the effects of single exposures and of exposures fractionated over two to eight days. In those studies we defined the probabilities of gastrointestinal and hematologic responses after promptly administered single and multiple exposures. We reported that the incidence of nausea and vomiting was diminished by a factor of about 2 when the exposure dose was fractionated, but that no diminution in hematopoietic damage was found. We have found further this year in studying the cases where the doses were given over periods of time greater than 8 days (many up to a year or more) that fractionated exposures within a week are as effective as a single dose equal to the sum of the fractions if the exposures are daily. This statement, however, is strictly accurate only if the exposures are greater than about 10 R/day. Our study reveals that there are multiple determinant variables whose relative importance varies for different physiologic and morphologic responses or effects in a manner not yet precisely defined. The principal determinants we have identified besides exposure size and total exposure period are: accumulated exposure in temporal subsets of exposures; number of fractions; average size of all fractions; average length of time interval between exposures; largest and smallest time intervals; and integrated average daily and weekly dose rate equivalents. Hematopoietic responses have been graphed out and quantalized where sufficient laboratory notes were found (603 of 1603 cases) to enable this type of effect to be related to these multiple variables. Similar relationships are being established for gastrointestinal effects. The multivariant analyses and cluster analyses are not as yet complete, but several salient facts about such fractionated exposures have emerged: there is little or no probability for vomiting if exposures are less than 10 R/day for less than 10 days. Such exposures, however, produce significant decreases in total WBC but not in the RBC or platelets. Exposures greater than 25 R/day when given daily accrue an increasing probability for vomiting to occur as 150 R is approached; the larger the individual fractions are and the smaller the radiation free interval is, the larger the probability for the occurrence of radiation sickness becomes. The precise dose-response relations for these interdependent variables are being derived. The basic retrospective study is to be finished this calendar year and the intramural report finished early in CY-70.

The following table is a list of the diagnoses in the patients whose hematological responses after fractionated irradiation exposures are being analyzed in the retrospective study.

The prospective study is focused on defining the radiosensitivity of man by observing directly the responses of man to radiation exposure wherever possible. Our previous studies (both retrospective of the clinical trials of others as well as prospective of 120 experiences of our own) have defined the probabilities of occurrence of human radiation-induced hematopoietic syndrome and prodromal symptoms from single exposures (see Radiobiologic Factors in Manned Space Flight, NAS-NRC, 1968). We have been extending our observations to radiation exposures prolonged in time by either protraction (constant irradiation with little or no radiation free interval during a day) or fractionation (rapidly delivered, daily irradiation with most of each day free of radiation exposure. In 1969, 10 patients were studied in this program bringing our total to 20 persons irradiated in the low-exposure rate facility (LETBI) and 10 persons in the medium-exposure-rate facility (METBI). The tables summarize these studies. All cases being treated at ORAU Medical Division with TBI are now either protracted in LETBI or fractionated in METBI. No single exposures in less than one day are now being done. Although the total number of patients treated with fractions is small, the individual studies have been conducted so carefully in depth that many facts bearing on the problem of men being exposed to space radiation are emerging:

1. An exposure of patients to 250 R in either system has a high probability (>>0.5) of causing serious if not fatal acute hematopoietic syndrome. This sensitivity varies with the nature of their disease.

2. Patients with polycythemia rubra vera after such an exposure develops a remission of symptoms and their abnormal red cell production ceases. Distinct clinical benefit has persisted for more than a year.

3. For the same total number of R the effects of daily fractionated exposures are more severe than those from daily protracted exposures, but less severe than those from a single exposure.

4. The dose rate dependence factor for human hematopoietic response is between 1.5 and 2.5 times (definitely not >2.5) the single exposure dose. For example, an effect that can be predicted for a single 100 R exposure in METBI is obtained by a protracted exposure in LETBI of >150 but <250 R. (Insufficient numbers of patients so far make it impossible to make the prediction more precisely.)

5. An incidence of four cases of severe acute hematopoietic syndrome among eight patients exposed at the 250 R dose level fix this amount of exposure as the upper limit of therapeutic tolerance in any present system unless greater dose-protraction (lower daily dose rates) or longer fractionated intervals are used. This high incidence of severe hematopoietic damage at this level of exposure underscores the hyperradiosensitivity of the patient suffering from blood dyscrasias and decreases the credibility of the greater than 450 R human lethal dose concept for normal man.

NUMBERS OF PATIENTS TABULATED ACCORDING TO KNOWN DIAGNOSES WHO RECEIVED THE THREE TYPES OF RADIATION EXPOSURE UNDER RETROSPECTIVE STUDY.

Acute leukemia		133
Lymphocytic	54	
Granulocytic	32	
Monocytic	10	
Stem cell	4	
Not otherwise defined (NOD)	33	
Chronic lymphocytic leukemia		320
Lymphocytic	312	
Aleukemia	1	
Leukemia (NOD)	7	
Chronic granulocytic leukemia		175
Granulo	171	
Monocytic, variant	4	
Lymphosarcoma		231
Lymphosarcoma	161	
Reticulum cell	30	
Lymphoma	27	
Giant follicular	12	
Thymoma	1	
Hodgkin's disease		168
Polycythemia rubra vera		96
Thrombocythemia		32
Blood disease, not otherwise defined (NOD)		5
		1160
Carcinoma (NOD)		331
Melanoma		17
Sarcoma		35
Renal disease (NOD)		16
Arthritis and musculoskeletal disorders (NOD)		35
		1594

TAB. .

LOW EXPOSURE RATE (1.5 R/Hr) TOTAL-BODY IRRADIATION OF PATIENTS

No.	Diagnosis	Sex	Age	Total Residence Hrs.	Total Residence Days	Total R†	Exposure Hours	Fractional Day (%)	Prodromal Symptoms
1	IT	M	61	116.0	4.8	150	100.0	86.2	0
2	CLL	M	76	73.1	3.0	100	66.7	91.3	0
3	CML	M	12	74.4	3.1	100	66.7	89.6	0
4	CML	F	45	78.7	3.3	100	66.7	84.8	Nausea
5	LS	M	79	76.2	3.2	100	66.7	87.5	0
6	CML	F	55	76.5	3.2	100	70.2	91.3	0
7	PRV	M	60	79.6	3.3	100	65.8	82.6	0
8	CLL	M	77	79.6	3.3	100	65.8	82.6	0
9	LS	M	62	201.5	8.5	250	170.0	84.4	0
10	CML	F	83	79.2	3.3	100	68.5	86.5	Nausea
11	CML	F	66	79.2	3.3	100	68.5	86.5	Nausea
12	PRV	M	61	203.7	8.5	250	171.8	84.4	0
13	IT	M	62	119.3	4.9	150	102.7	86.5	0
14	PRV	F	59	176.5	7.4	230	153.9	87.2	Vomiting
15	PRV	M	75	208.3	8.7	250	169.1	81.1	0
16	LS	F	59	207.3	8.6	250	165.8	80.0	0
17	LS	M	55	194.1	8.1	250	163.4	84.2	0^*
18	LS	M	63	197.6	8.2	250	163.4	82.7	0
19	PRV	F	77	199.5	8.3	250	165.6	83.0	0
20	CML	M	52	211.2	8.7	250	164.5	77.9	0

Diagnoses:

IT (Idiopathic thrombocythemia)
CLL (Chronic lymphocytic leukemia)
CML (Chronic myelocytic leukemia)
LS (Lymphosarcoma)
PRV (Polycythemia rubra vera)

† R to Rad conversion factors:

Midline dose - 0.54 Rad = 1 R
Epigastric dose- 0.52 Rad = 1 R

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3. Progress in CY-69: (continued)

Our system of humanoid phantom dosimetry utilizing minute LiF rods has proven this year to be basic for equating various biologic responses with exposures and doses in the two facilities. It enabled us to show that equal exposures in the two facilities produce depth doses in some target organs that differ by more than 20%; that surface dosimetry has an unpredictable relation to depth dose unless the radiation direction is constant, unidirectional and known; and that, at present "dose" to various sized persons in the same measured field is not determinable. We are presently making some 20 surface measurements on each patient irradiated. We aim to correlate these measurements with various body size parameters (e.g. weight, thoracic and abdominal diameters) to enable dose prediction for deeply seated organs from surface exposure measurements alone. Our data collected so far is not sufficient for sound statistical analysis, since number of patients is relatively small and a series of different size humanoid phantoms is not yet available for this purpose.

A series of experiments with humanoid tissue equivalent phantom containing several thousand dosimeters in a 3-dimensional array enabled us to measure many organ doses for an average normal man in both LETBI and METBI. The following table lists these organs and the average dose and dose range. The bone marrow average dose was 64% of the field exposure dose but as shown in the next table the range of doses to the various bone marrow compartments was 0.54 rads to 0.78 rads/R of TBI, a range greater than that in any other organ. ast bone marrow dose was found to occur in the sacral vertebrae instead of the thoracic ones as previous studies with water-filled phantoms have indicated. The great variability we found in bone marrow compartment dose may be accentuated by deviations in body configuration and mass and probably explains the great variability we find in hematologic response among patients with the same disease exposed to the same dose.

Physiologic monitoring has been done on the LETBI patients with an electronic computerized system patterned after the one at the Houston Manned Space Craft Center. Our paper describing the use of power spectral analysis as a statistical system for data reduction of pulmonary impedance signals was published and received favorable comment from around the world. We completed a series of experiments in normal subjects to observe damping of respiratory movements by external weights. We found that weights up to 10 pounds failed to change the power spectrum of pulmonary impedance waves, if the subject was not distracted by external stimuli but led to fatigue-like breathing within the two hour test period if he was. The low incidence of nausea and vomiting among the LETBI patients again prevented our observation of reflex vagal effects upon either pulmonary impedance or EKG R-R interval length. A new data reduction system was devised and programmed for computer computation for analysis of EKG R-R interval. In this system an EKG trace of any length is reduced to a histogram (automatically graphed out) of the occurrence frequency of the various R-R intervals present in that EKG trace segment. The histogram allows the physician to see at a glance cardiac rate, beat-to-beat variance, and cardiac regularity. Experiments with human subjects exercising produced histograms showing that stress causing tachycardia

TABLE

ORGAN DOSES IN TWO TOTAL-BODY IRRADIATION FACILITIES

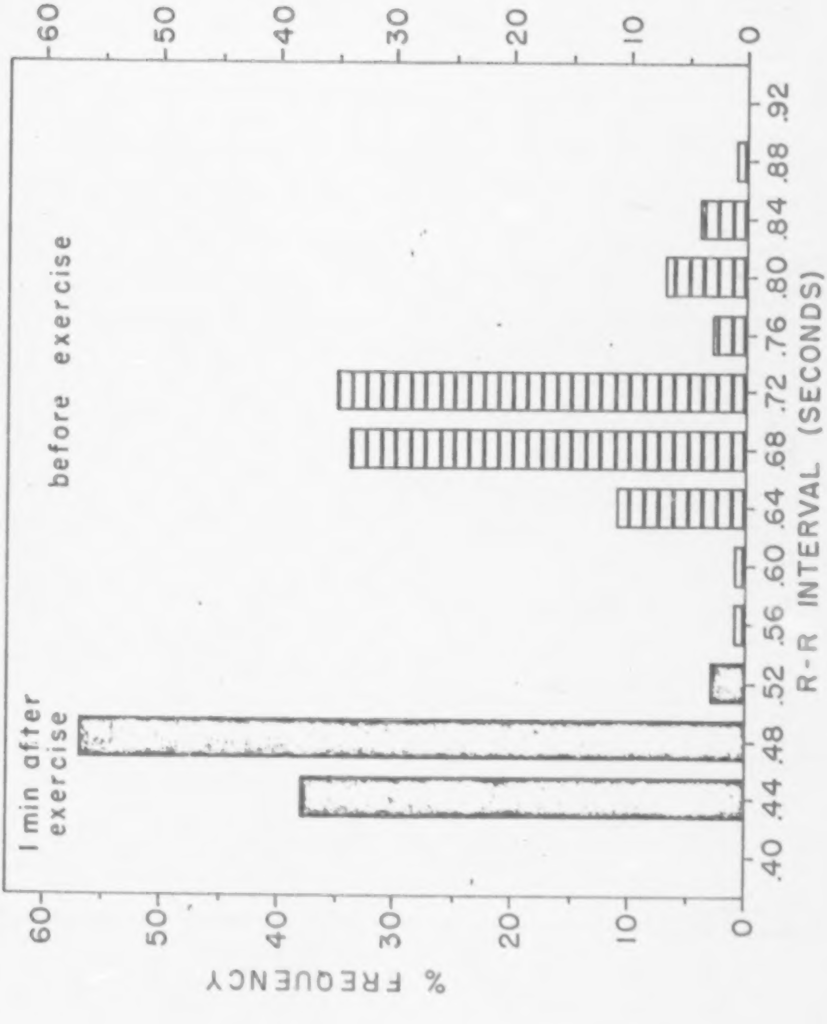
Organ	Number of Dosimeters	Dose in Rads/100 R at Center of Exposure Field METBI		LETBI	
		Average	Range	Average	Range
Abdomen	34	64	59-69	52	47-58
Bone marrow	137	64	53-86	58	40-90
Cerebellum	9	77	74-81	75	72-77
Cerebrum	21	75	70-79	78	74-83
Heart	16	65	58-70	63	58-71
Intestines	107	67	54-76	54	46-61
Kidneys	6	66	62-70	52	51-54
Lenses of eyes	2	87	85-90	90	89-92
Liver	42	67	61-78	59	53-68
Lungs	185	67	58-77	64	56-77
Skin (above sternum)	2	73	72-75	82	80-83
Skin (front waist)	2	74	72-75	74	73-75
Spleen	7	69	64-73	55	53-57
Thyroid	2	76	75-77	78	76-80

TABLE

COMPARTMENTAL AND AVERAGE ACTIVE BONE MARROW DOSE

Marrow Compartment	Fraction of Active Bone Marrow* (%)	Number of Measurements	METBI Average Dose (Rads/100R)	METBI Weighted† Factor	LETBI Average Dose (Rads/100R)	LETBI Weighted† Factor
Head[a]	13.1	12	78	1022	80	1048
Upper Limb[b] Girdle	6.4	16	66	422	66	422
Sternum	2.3	2	69	159	72	165
Ribs	7.9	26	68	537	60	474
Vertebrae[c]	28.4	41	65	1846	57	1619
Sacral Vertebrae	13.9	5	54	751	43	598
Lower Limb[d] Girdle	26.1	32	59	1570	50	1305
Totals	98.1[e]	137		6277		5632
		Average Dose	64		57	

a - Includes cranium and mandible
b - " scapulae and clavicles, does not include humeri (see "e")
c - " cervical, thoracic, and lumbar vertebrae
d - " pubic, ilial, ischial bones, femaral head and neck
e - Reflects the absence of measurements in the humeri where 1.9% of active marrow is located
* - See Reference 9
† - Weighted factor = Average dose x Percent bone marrow



NORMAL SUBJECT'S CARDIAC R-R INTERVAL RESPONSE to EXERCISE increases cardiac regularity in normal young subjects but not in patients or persons in situations where respiratory disease and other abnormalities limit exercise tolerance through relative anoxia. A portable monitoring system similar to that in LETBI was engineered and purchased and is in process of being installed for use in the METBI facility where the 90 R/hr (vs the LETBI rate of 1.5 R/hr) has caused gastrointestinal distress with predictably high frequency.

In searching for new laboratory criteria or measurable nonlethal "end-points" of radiation effects we worked with three systems, two of which are in use in the clinical laboratory of the Lunar Receiving Laboratory, NASA, Houston - electronic RBC sizing and distribution studies and RBC osmotic fragility distribution using an automated fragillometer. The third system is biochemical measurement of circulating anti-proteolytic enzyme levels. No anti-enzyme measurements have been made as yet in man; we are first setting up the method using the sera of animals exposed to large single fatal doses of radiation known to destroy these substances before death occurs.

In electronic RBC sizing, we developed a method of treating blood with glutaraldehyde that quickly "fixes" individual RBC size without distorting RBC volumes. These fixed RBC particles can be used indefinitely as reference standards. Since they are easily and simply prepared, such a standard can be made for each person whose RBC are going to be remeasured later after exposure in situations that change the kinetics of RBC production (e.g., high oxygen atmospheres, radiation damage to bone marrow, metabolic damage, RBC precursors, etc.). This system was used in studying the hematopoietic responses of the LETBI and METBI patients (and also, see below, the responses of mice in our dose-rate biologic dosimetry system being developed in LETBI). The results were analyzed by the Delta-Square (Δ^2) Mathematical Test for RBC normality. The Δ^2 for patients with PRV was found to change progressively after TBI and to reflect accurately the amount and kind of RBC production present at the moment. Remissions after treatment of over a year in length were graphed by this method. In persons without RBC disease the Δ^2 did not change significantly after exposures of 100 to 150 R. A preliminary report of these studies appeared in the 1968 Progress Report published in July 1969, pp. 112-118.

The severe hematopoietic responses that were obtained with 250 R exposures in both the METBI and LETBI suggest that the 60-fold reduction in dose rate in the LETBI facility is insufficiently low to allow normal hematopoietic tissues to repair while malignant tissues that are not under homeostatic control would be prevented from recovering from radiation damage. A literature search for information bearing on this problem revealed two opposing unresolved views about whether there is a biological difference that can be recognized between the effects of rapidly delivered daily fractional radiation exposure (as in METBI) and slowly delivered all-day irradiation (as in LETBI). Intuitively it would appear that a longer radiation free interval would allow more radiation damage to be repaired before the next exposure; that radiation damage being constantly produced would be poorly repaired unless the damage cumulated at a rate slower than inherent repair mechanisms can operate.

2. Project Title: Radiosensitivity in Man:
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15. Progress in CY-69: (continued)

Our human radiotherapy studies this year indicate that even though there is a 23+ hour radiation free interval in fractionated exposures in METBI, the effects produced there are more severe and so less damage per R is repaired there than after a similar sized daily dose given slowly in 20+ hours/day in LETBI. One interpretation of this divergence might be that 30 R/day delivered at 1.5 R/min (60+ minutes) causes more total damage than 30 R/day delivered at 1.5 R/hr so that more residual unrepaired damage remains each day even though repair rate in the long radiation free interval is more rapid than that during constant radiation exposure.

In the contextof radiation exposure profiles being considered for medical management of space exploration (see Table, page 19), we need to know the relative rates of accumulation of unrepaired radiation damage in fractionated vs protracted irradiation to allow prediction of the degree of sensitization that the crew may have developed to later exposures to unpredictable bursts of solar radiations. This 3-dimensional dose rate problem could be solved by establishing the radiation damage/repair equilibria for several organic systems important to the body's recovery. While our studies suggest that at 30 R/day in LETBI man's gastrointestinal system is kept repaired during 8 days of nearly constant irradiation, the severe damage that accrues during this time in the bone marrow prevents us from proceeding to more prolonged periods of exposure and a greater than 250 R "dose" to determine how long this apparent gastrointestinal equilibrium can be maintained. We, therefore, reverted to the use of mice to avoid these constraints of human radiation exposures to determine the level and endurance of the gastrointestinal and bone marrow repair equilibria at 30 R/day of protracted versus fractionated radiation in our two facilities. A feasibility experiment was done to see what the criteria might be for determining the establishment of such equilibria when usually available laboratory methods were used for assessment. Much to our surprise we found that the mouse (a species that is at least twice as radioresistant as man) cannot tolerate (i.e. establish hematopoietic equilibria) an exposure rate of 1.5 R/hr or 30 R/day, the level of exposure in LETBI. At this rate of exposure we found abundant evidence of a reparative attempt in the erythroblastic tissues of the mouse spleen (but not in the bone marrow) and death ensued in 70 to 90 days at this exposure rate from severe megaloblastic anemia. Normal daily rate of gain in weight was maintained by the mice at this exposure rate but not at the doubled rate (3.0 R/hr). A questionably adequate white blood cell and platelet count was maintained by then only below exposure rates of 0.8 R/hr (∿15 R/day). While extrapolation from these experimental observations in mice to man is most likely invalid, they suggest that an indefinitely protracted exposure level of less than 0.25 R/hr (250 mR/hr) or less than 5 R/day is the upper limit of radiation exposure whose effects man could be expected to surmount through establishing a new level of cellular kinetic equilibrium.

POSSIBLE SPACE RADIATION PROFILES FOR VARIOUS MISSIONS

I. Earth Orbits	Upper Estimates Rads/day	Upper Estimates Rem*/day	60-Day Dose Approximations (Rads) Skin	60-Day Dose Approximations (Rads) Depth
a. Circular	0.04	0.05	3.0	1.0
b. Elliptical	7.6	14.6	450-870	145-220
c. High** Elliptical	9.8	18.8	575-1120	200-420
d. Synchronous				
Maximum (1 day)†	34.2	38.0	30-40	10-20
No flare	4.2	8.2	240-480	60-120
Total mission	-	-	270-500	100-150

* Assumes QF of 2 for medium energy electrons of inner Van Allen belt.

** Apogee 2000-5000 miles.

† Considers occurrence of Class III flare and abortion of mission as soon as possible.

II. Moon Exploration	Rads/day	Rem/day	Mission Dose Skin	Mission Dose Depth
a. No flare*	0.04	0.05	0.3-0.4	0.1
b. One flare† (CSM) one day	0.04+30	0.05+60	100	25
c. One flare (exposure in LM or lunar surface)	0.04+350	0.05+700	350	100

* Galactic radiation and Van Allen belt electron exposure only with 5 gm/cm^2 shielding in command ship (CSM).

† Class III flare producing 40 MeV protons and alphas (lunar ship (LM) with 0.25 gm/cm^2) causes abortion of mission as soon as possible.

[Modified from data in Radiobiological Factors in Manned Space Flight (Langham, ed.) and unpublished manuscript of John E. Pickering, Radiobiological Concepts for Manned Space Missions, 1969.]

16. Program Plans for CY-70:

The retrospective study of human hematologic and gastrointestinal responses from past therapeutic trials throughout the USA will be summarized in a detailed intramural report. Analyses of the long-term fractionated exposure data are now almost complete in this phase of our search for dose-response relations meaningful in the context of possible radiation exposure in space. The variable relative importance of the following exposure factors will be determined by cluster analysis and probability statistics: total daily exposure, exposure rate, radiation free interval, fractional size of exposure, previous exposure history, and uniform (total) versus non-uniform (partial) body exposure. This detailed report of this phase of the retrospective study will include Part I, single exposure, Part II, multiple fractionated exposures over 8 days, Part III, multiple fractionated exposures for periods longer than 8 days, Part IV, multiple fractionated portal (partial body) exposure, and Part V, continuous total body exposure. The overall nature of the human irradiation data stored in the taped digital information data bank will be summarized so that in the future attempts can be made to answer other questions that may arise about human dose-response relations. Summarization reports will be made of this study for the open literature after its initial submission to NASA Manned Space Craft program directors and the Division of Biology and Medicine of AEC. Other open literature reports, presently being written, to be completed in CY-70, are on the LETBI facility and its utility in human radiation therapy and radiobiology, the LETBI dosimetry systems; the LETBI physiological monitoring system and our initial physiologic studies; and new data processing and computational programs that we have developed to assist these analyses and their interpretation.

The "Prospective" Human Radiation Sensitivity studies will be continued at least at their present level in the LETBI facility and will be increased in number in both LETBI and METBI as more patients appropriate to this type of therapy are referred to us by our consultants. An active canvassing program for increasing our utilization of these facilities has been developed using the mail, semipopular medical news releases, scientific journal articles, and formal talks at scientific and medical meetings. We anticipate that this program will produce a greater influx of patients than we have experienced in the last two years. Our laboratory studies of human effects of radiation exposure will be broadened to include urinalysis for protein degradation products, serum proteolytic enzymes and inhibitors, acid hemolysis sensitivity of RBC, serum ^{59}Fe disappearance rates, oral-iron demand, and survival and kinetics of tritium-labeled lymphocytes and leukocytes. Where possible, the data from these studies will be processed and analyzed by computer programs either newly devised or adapted to our system.

Dosimetry. We will attempt to develop a combined energy dependent as well as independent dosimeter that can be worn in spatial array so that individualized depth doses can be determined in different sized people exposed to identical radiation fields. A serious error at present in all studies of dose-response relations results from our inability to equate various body configurations and bulk with film badge exposure for derivation of a depth dose (reflecting body mass) in some deep seated internal target organ. This dosimetry problem becomes more complicated when exposure is from some unknown direction and various portions or surfaces of the body are shielded (e.g., by equipment, machinery, or the heat shield of the space vehicles). Our object is to develop a system using minute external sensors that can be worn on the skin to measure the nonuniformity of radiation exposure and thereby enable compartmental body doses to be derived so that the proper safety or "dose reduction" factors can be chosen and applied to each radiation experience.

We will continue to explore the usefulness of the NASA-SCS physiologic monitoring system in the irradiated and sick patient, attempting to derive additional real time data-analytical systems that will obviate the need for physicians to personally monitor miles of traces for signs of distress and illness. Use will be made of oscilloscopic display units that can respond to push-button demands for stored trace segments or computed values for instant comparison with present values of the subject's physiologic signals. To increase the sensitivity of this system to detect peripheral vascular reactions to radiation and stress, instrumentation will be obtained for measuring skin galvanic response for simultaneously correlation with the other physiologic parameters being monitored. Our progress in relating changes in R-R interval and pulmonary impedance with various levels of physical activity now permits us to study radiation-induced fatiguability directly with time honored ergometric methods in parallel with the electronic system. Several instances of extreme fatiguability occurred this year in patients exposed to less than 30 R/day at the METBI rate. No such responses were observed in the LETBI exposures. Whether such radiation-induced fatiguability has a large psychic overlay will be determined by analysis of cardiac, respiratory, and skin response to standard exercise on an ergometer.

We will continue to search for mathematical models derivable from clinical and experimental radiobiologic observations for use in explaining the reduced effectiveness of constant low-dose-rate exposure and fractionated high-dose-rate exposure with short or long radiation free intervals. Expendable laboratory animals will be used when doses and rates must be studied that would prevent our studying them directly in man because they would be either dangerous or insufficient for therapeutic purposes. Simultaneous human and mouse radiation exposures in LETBI and METBI will be made to compare the responses of the two species directly and to try to develop a biologic dose-rate dependent dosimetry system that can be used to predict and explain human responses under various low-dose-rate/total-dose combinations of exposure.

Large animal studies at UT-AEC Agricultural Research Laboratory, Oak Ridge, have now proven the safe operation of their recently constructed high exposure rate cobalt-60 total-body irradiation facility (HETBI). This irradiator has been made available to us to study the therapeutic effectiveness of high exposure rates in man. The maximum exposure rate appears to be about 50 R/min. We propose trials with this facility in which we would expose patients with chronic granulocytic leukemia (CGL) to 50 R TBI. Our studies in LETBI and METBI appear to show a remarkable dose-rate dependence of the bone marrow granulocytic precursors in persons with this disease: In LETBI, protracted 100 R exposure (1.5 R/hr) produce little or no demonstrable effect; in METBI, 100 R exposure (90 R/hr) produce clinically acceptable amelioration of the disease and a prolonged period of suppression of total white blood cell count. To obtain an hematopoietic effect of similar degree in LETBI, the required exposure is predicted to be more than 150 R but less than 250 R. Clinical studies of patients with CGL exposed in this dose range in LETBI are in progress. Exposure trials in HETBI (3000 R/hr) will be initiated at the 50 R level. Studies of the effectiveness of this dose at this dose rate will provide the third dose-rate effectiveness data point necessary to test the most modern radiobiologic concept (Bateman) that radiation damage/R is proportional to the reciprocal of the cube root of the dose-rate. This mathematical relation appears to describe adequately the dose-rate dependence of human skin damage and animal radiation lethality. It is not known whether it can be used to predict all nonlethal human total body and cellular response relations to dose. Our study will provide human medical, physiologic, and laboratory data bearing on this question directly and should provide an improved clinical basis for evaluation of the human radiation-exposure constraints suggested by the Space Radiation Study Panel Report of the National Academy of Sciences (1967). Safe operation of the HETBI facility for exposure of patients will be based upon stringent health physics practices and pre-trial dosimetry studies with humanoid phantoms. The same lithium fluoride dosimetry techniques will be used in HETBI as are now being used to measure the exposures of patients in LETBI and METBI.

Progress in basic, experimental immunology of tissue transplantation at ORAU Medical Division and elsewhere has enabled us to develop plans to begin the clinical study of survival of homologous bone marrow grafts and their therapeutic utility after 400 R TBI in patients with acute leukemia, late chronic lymphocytic leukemia, and the blast crisis of chronic granulocytic leukemia when other therapeutic modalities have been ineffective. Measurements and observations on the clinical course and hematopoietic changes after irradiation and bone marrow transplantation will be made by the NASA study group to obtain human radiobiologic and physiologic data relevant to this form of therapy, on the repair rate of near lethal human total-body irradiation (e.g., like that which could occur during extravehicular activities in space from the unexpected occurrence of a large solar flare or in an accident resulting from the use of nuclear energy propulsion systems.)

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17. Program Plans for CY-71:

By 1971 sufficient experience with patients at 1.5 R/hr (LETBI) and various fractionated exposure schedules will have been obtained along with parallel exposures of mice to permit knowledgeable choice of minimal dose rates, doses and radiation-free intervals for improving therapeutic results. These exposure factors need to be alterable according to some schema to fit the needs of each case. The obverse of this therapeutic progress will be our increased ability to predict more accurately the extent of probable radiation damage to normal men exposed according to various conjectured scenarios or actual space (or accidental) radiation conditions. For example, our retrospective human studies and our preliminary mouse low-dose-rate study raise the possibility that the present low-exposure-rate and daily dose in LETBI (1.5 R/hr//30 R/day) may be about three times higher than necessary to obtain desirable therapeutic effects without causing damage to normal cellular systems. If the results of these studies prove to be true, the "tolerable" constant low-dose-rate for man would be expected to be less than 0.1 R/hr, a value that approaches closely the average exposure rates that can be expected to be endemic in some areas of space exploration. Long-term therapeutic trials at dose rates of 0.5 R/hr or less and daily fractional dose sizes of about 10 R will need to be done and their effects studied carefully. Our therapeutic efforts with TBI have up to now emphasized fairly long (weeks or months) periods of observations of the effect of a single exposure experience. We now believe we are ready to use regularly spaced, carefully selected, repeated small exposures over a period of many months in an effort to maintain more uniform control of disease and possibly a greater relative effect upon abnormal cell systems in contrast to normal ones. We will use therapeutic irradiation scenarios derived in part from "space radiation profiles" (see Table, page 19). These may be based either on intelligent conjectures or actual experiences measured in space (e.g., telemetered radiation flux measurements from unmanned exploratory vehicles in space beyond the moon).

The total accumulated human radiation-effects data derived from these studies will be under continuing statistical reassessment to increase precision in these measurements of man's radiation tolerance. Precise knowledge here can increase clinical confidence in the relative importance of the space radiation hazard and in combination with real temporal profiles of radiation levels in space, can be used in design evaluation of the shielding requirements for various types of space vehicles still in planning stages.

Chemical means of protecting normal cellular systems from radiation damage and of enabling them to repair faster than abnormal cells will be tested directly in man to see if protection is afforded under the conditions of protracted irradiation. The FDA feasibility studies for human use of these drugs will have been completed by CY-71. If successful, they will allow the trial of such radioprotectant drugs as "WR-638" and "WR-2721" (sulfahydril containing hydrocarbons (thiols) in combination with phosphoric acid) in our radiotherapy patients to determine protection of normal tissues can be increased under conditions of chronic low-exposure rates. Such studies in LETBI and METBI would enable us to predict the usefulness of such drugs by astronauts on extended space missions where high flux Class III solar flares have a credible probability for occurrence at unpredictable times. These drugs in mice are effective by about a factor of 3.0 ($LD_{50/30}$ of undrugged mice = ~800 R; $LD_{50/30}$ of drugged mice = ~2400 R) within

Schedule 189
2. Project Title: Radiosensitivity in Man:
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17. Program Plans for CY-71: (continued)

30 minutes of administration. If these times for absorption and tissue deposition were required for man, there would be ample time with the present solar flare detection and communications systems for an astronaut to ingest and absorb the drug to reduce his sensitivity to an unavoidable exposure to a large flare.

18. Significant Capital Equipment:

	CY-70	CY-71
Ergometer system	$ 4,000	
Skin galvanic response	4,000	
Respiratory gas analysis and blood pressure monitor		$ 5,000
Colorimeter	1,000	
Microscope	1,000	
Computer interfacing and remote readout system	5,000	5,000
Humanoid phantom dosimetry system	5,000	5,000

SCHEDULE 189

ADDITIONAL EXPLANATION FOR OPERATING COSTS

Oak Ridge Operations
Field Office or Laboratory

40 04
Budget Activity No.

1a. Contractor: Oak Ridge Associated Universities

1b. Contract No.: AT-(40-1)Gen-33

2. Project Title: Radiosensitivity in Man: A Study of Therapeutic and Accidental Whole-Body Irradiation - NASA

3. Project No.:

4. Starting Date of Project: Continuing

5. Date Schedule Prepared: November 30, 1972

6. Method of Reporting: Annually

7. Working Location: Oak Ridge, Tennessee

8a. Person in Charge: G. A. Andrews, R. M. Kniseley

8b. Principal Invesitgators: C. C. Lushbaugh, G. A. Andrews, R. M. Kniseley, C. L. Edwards

9. Man Years:	Funded CY 1972	Estimated CY 1973	Estimated CY 1974
	7.25	7.25	7.25

10. Funding and Costs:	Estimated CY 1972	Estimated CY 1973	Estimated CY 1974
Funding			
Prior Year Unexpended Funds	$ 8,800	$ 7,300	$
Current Year Funding	160,000	160,000	183,000
Total Funds Available	$168,800	$167,300	$183,000
Costs			
Personnel Services	$104,500	$110,000	$113,500
Travel	2,300	2,000	2,000
Materials and Supplies	3,500	3,000	3,000
Computer Services	1,800	4,000	4,000
Equipment	900	0	8,000
Technical Services	2,500	1,300	1,500
Overhead	46,000	47,000	51,000
Total Costs	$161,500	$167,300	$183,000

2. Project Title: Radiosensitivity in Man:
A Study of Therapeutic and Accidental
Whole-Body Irradiation

3. Project No.:

11. Dates and Titles of Publications:

See 189.71 for list of publications prior to 1972. A complete list of publications and a list of available computer programs generated by this study are listed in *San Antonio Briefing Material Booklet*, circulated March 23, 1972.

43. Ricks, R. C., Lushbaugh, C. C., McDow, E., and Frome, E.: *Pulmonary-impedance power spectral analysis: A facile means of detecting radiation-induced gastrointestinal distress and performance decrements in man.* Proc. National Symposium on Natural and Manmade Radiation in Space. NASA TM X-2440. pp. 238-248, January 1972.

44. Yuhas, J. M., Stokes, T. R., and Lushbaugh, C. C.: *Multifactorial analysis of human blood cell responses to clinical total-body irradiation.* Ibid. pp. 233-237.

45. Beck, W. L., Stokes, T. R., and Lushbaugh, C. C.: *Dosimetry for radiobiological studies of the human hematopoietic system.* Ibid. pp. 974-980.

46. Lushbaugh, C. C.: *Predicted levels of human radiation tolerance extrapolated from clinical studies of radiation effects.* Ibid. pp. 398-415.

47. Lushbaugh, C. C. and Ricks, R. C.: *Some cytokinetic and histopathologic considerations of irradiated male and female gonadal tissues.* Proc. Symposium Mt. Sinai Cancer Clinic, 1970. University Park Press, 1972.

48. Beck, W. L., Cloutier, R. J., and Watson, E. E.: *High-dose monitoring of personnel with film and TLD.* Health Physics Journal, 1972 (in press).

49. Yuhas, J. M., Stokes, T. R., and Lushbaugh, C. C.: *Radiosensitivity and recovery potential of human blood forming tissues.* Am. J. Roentgenology and Radiotherapy, December 1972 (in press).

50. Ricks, R. C., Lushbaugh, C. C., and Frome, E.: *Measurement of performance decrement by impedance pneumography during controlled exercises and total-body irradiation in man.* Aerospace Med. Assoc. J. (submitted for publication).

51. Lushbaugh, C. C.: Chapter 10, Radiosensitivity of Man. In Tobias, C. and Todd, P., *Space Radiation Biology*, Academic Press, 1972 (in press).

52. Ricks, R. C., Lushbaugh, C. C., and McDow, A. E., Jr.: *Pulmonary impedance power spectral analysis: Its correlation with heart rate and expired* CO_2 *during exercise stress in man.* J. Assoc. Adv. Med. Instrum. 6: 186, 1972 (abstract).

11. Dates and Titles of Publications: (continued)

53. Stokes, T. R., Lushbaugh, D., Humason, G., and Lushbaugh, C. C.: *^{59}Fe studies on the erythroblastic response of normal and splenectomized mice to low-level continuous radiation.* Rad. Res. 51: 471-472, 1972 (abstract).

54. Ricks, R. C. and Lushbaugh, C. C.: *Changes in serum creatine phosphokinase (SCPK) levels following total-body irradiation in man.* Aerospace Med. J., 1972 (abstract, in press).

55. Beck, W. L., Stokes, T. R., and Wade, L., Jr.: *Dosimetry for a total-body irradiation accident.* Health Physics 23: 419, 1972.

56. Beck, W. L., Stokes, T. R., and Lushbaugh, C. C.: *Dosimetry for Total-Body Irradiation Therapy.* Health Physics, 1972 (in press).

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12. Objective and Scope:

The objective of this study is to glean from human accidental and therapeutic irradiation cases all pertinent radiobiologic information for reappraising and improving our knowledge of man's radiosensitivity. This study is cooperative with the AEC-supported study of the use of total-body irradiation as a therapeutic modality for some human blood dyscrasias. Where the AEC study concerns itself with clinical aspects, the NASA study is directed toward extracting measureable information on biologic endpoints of radiation effects. Study areas that are receiving major emphasis are: hematology, gastrointestinal side effects, dosimetry, and physiologic monitoring.

The need for more quantitative information on the effects of low radiation doses and low-dose rate exposures is generated by programs that involve manned space flights. The plans for space laboratories expand the number of persons at risk from the low doses of natural space radiation and include the possibility that an additional risk may arise from manmade radiation associated with the use of nuclear power systems. Our studies are intended to strengthen the confidence we presently have in our knowledge of man's ability to repair radiation damage so that AEC, FRC, NASA, and other governmental agencies can establish nonoccupational permissible radiation exposure levels and continually review and update NASA occupational career limits for radiation-exposure of astronauts as required for engineering design of advanced systems. Our knowledge of the effects of larger radiation exposures at high and low dose rates is growing substantially, but is as yet inadequate for deriving dose/response equations that allow high-confidence predictions of the amount of acute and chronic damage that can be expected from small doses to the total body or its parts. Extrapolations that estimate effects from extremely low exposures accumulated over long periods of time on the basis of studies of high exposure sustained in short periods of time, derive all of their justification from radiobiological studies of lower

2. Project Title: Radiosensitivity in Man: A Study of Therapeutic and Accidental Whole-Body Irradiation

3. Project No.:

12. Objective and Scope: (continued)

mammals (chiefly mice). Some observations indicate that after a 5 to 10 rad dose, for example the probability of a serious consequence occurring in an individual's life time is so low that a threshold concept is valid for practical regulatory purposes. Additional unbiased clinical observations are, however, sorely needed to defend existing environmental and occupational radiation-exposure constraints from attack by well-meaning, but impractical, theorists.

13. Basis of Cost Estimates:

The cost estimates are based upon program expenses through December 1972 and projections through December 31, 1974.

The major portion of the budget is expended now upon supporting medical research personnel engaged in progressive as well as retrospective research. Equipment needs are low in comparison to previous years. One physician (C. C. Lushbaugh) of the four listed as Principal Investigators (page 1) is almost full time; the others are supported entirely by the AEC budget. In addition, the staff on this project consists of the following full-time personnel: a Ph.D. physiologist (R. Ricks); a radiobiologist research assistant (T. Stokes); a nurse (M. Rogers); and a technician-console operator (A. Sipe). Additional support is obtained from persons supported in whole or in part by the AEC budget: computer supervisor/analyst, electronic engineer, electronic technician, hematology research associate and technician, biochemical technicians, nursing supervisor, and cytogenetic research personnel. This staff is now equivalent to seven man years.

Out physiologic monitoring capabilities were successfully integrated in 1971 with a bicycle ergometry setup and in 1972 with serum CPK analysis and alveolar CO_2 measurement. These changes have enables us to develop a test system for studying whether or not small total-body radiation exposures alter physical endurance, reduce respiratory efficiency, and cause fatigue.

Travel expense is budgeted on the assumption that ORAU staff personnel working on this project need to be involved in pertinent radiobiologic conferences, trips to contributing institutions for dosimetry studies, and to collaborating government agencies who have mutual interests in protecting man from radiation hazards. Dr. Lushbaugh continues as an active member of the Radiation Study Panel of the Space Science Board of the National Academy of Sciences that is presently studying the HZE particle problem.

Computational costs for data management have been kept remarkably low by the development and operation within the Medical Division (largely with AEC support) of a unique data analysis system based on an IBM-1800 real-time computer. The documented programs that have been created or modified for use in the NASA study are listed under "publications" in 189:1972 submitted October 1971 and in the *San Antonio Briefing Booklet*, March 1972. These programs are available to other users. Acquisition of a Calcomp plotter and development of data input

2. Project Title: Radiosensitivity in Man: A Study Of Therapeutic and Accidental Whole-Body Irradiation

Project No.:

13. Basis of Cost Estimates: (continued)

methods now enable us to obtain hematologic time graphs, pulmonary impedance power spectral graphs and other kinds of clinical and laboratory responses in matters of minutes; this has greatly relieved our need for drafting work by hand. The ORAU system still does not have the capacity for holding the entire NASA/AEC Data Bank of Human Radiation Effects even though it was greatly reduced in bulk by diligent house cleaning and reorganization this year. Retrieval of data for analysis and its compilation still will require rental time on the Oak Ridge National Laboratory's large (IBM 360 series) computers until we can convert to greater disk storage. Loss of a salaried programmer in 1972 has put us on a pay-as-you-go computational basis for 1973. Loss of a health physicist stopped our development of personalized dosimetry and reduced our dosimetry to technical determinations only of daily exposures.

14. Relationship to Other Projects:

Forty-two U. S. medical centers have cooperated in this program by providing clinical data from patients previously treated with total-body irradiation. Many of the physicians and radiation physicists who participated in these therapeutic studies originally continue to collaborate with us as our study develops. At the moment, Dr. J. del Regato and staff (Colorado Springs) are preparing a report of the effect of fractionated small doses on their patients whose data was retrieved for them from our Human Data Bank. Dose-response relations derived from such studies are reported to the Space Radiation Study Panel of the National Research Council of the National Academy of Sciences in addition to the Preventive Medicine Division, Manned Spacecraft Center.

In addition to the collaborations previously reported with others interested in human radiation effects (see AEC 189/1969 submitted to AEC and NASA, October 1968), we are cooperating on a mutual basis with the Radiobiology Section, Brooks USAFB, the AEC/NSF collaborative effort to exchange information with Russia on space radiation and its effects, USAEC Division of Safety and AFSWP training courses in medical management of radiation accident victims and casualties, and NCRP, Committee number 14, Study of Decision Making During a Radiation Emergency.

Our project continues its strong crossties within the Medical Division with the clinical personnel of the radiotherapy and clinical investigation sections who are studying mechanisms of radiation injury under ORAU's AEC contract AT-(40-1)GEN-33. No charges are made against the NASA budget for the clinical staff's support of the LETBI and METBI studies in which the patients require extensive medical and nursing care on a 24-hour basis for periods of time up to 42 days. In addition, a mutually cooperative study has been arranged without additional cost to NASA for determining what levels of single, repeated, or protracted irradiation exposures result in alteration of the bacteriologic flora of the persons exposed. This study has received its main financial support from the Army, but is also supported by the AEC budget. The AEC completed in 1970, for the Medical Division's use, a laminar air-flow sterile, 2-bed hospital ward for the care of persons without adequate bone marrow production of blood cells as after total-body irradiation or other bone marrow injury. The NASA

14. Relationship to Other Projects: (continued)

personnel cooperated with the AEC staff in the third high dose, bone marrow transplant in man this year and continues studying the course of a normal young man accidentally exposed to ^{60}Co gamma rays (260 R) in 1971.

15. Progress in CY-72:

A. Prospective Studies

We previously reported 51 successful radiation exposures in the low-exposure-rate total-body irradiation facility (LETBI at 1.5 R/hr) (see 189.1961, 189.1970, and 189.1971). In Table 189.1972 we list the twelve new patients studied this year. These patients bring the total number to 63 that have received low-dose-rate total-body irradiation in the LETBI facility built by AEC for this study (furnished and equipped by NASA funding on this project). In addition, as proposed in 1970, the therapy plan has been modified to include study of the effects of only 10 R/day instead of the usual 30 R/day exposures. Ten persons have now received this kind of treatment given in 6.7 hours during their sleep. Patient acceptance is high. Several patients have tolerated well 20 days of 10 R/day exposure given daily 5 days/week for 4 weeks. We find that at this rate of exposure the marrow can quickly repair accumulated damage and return peripheral blood counts to previous levels.

During 1972 we have had 22 suitable patients for comparable fractionated doses at the more rapid rate of 1.5 R/min in the medium-exposure-rate total-body irradiator (METBI) as planned. These 22 exposures are summarized in the table along with the 12 new LETBI cases to compare types of exposure and doses. The development of this irradiation modality enables us to make better comparisons of the effect of fast (1.5 R/min) and slow (1.5 R/hr) exposures. Total body dose is being kept the same in both irradiators where formerly in METBI the whole dose (up to 200 R) was usually given promptly in less than one day. The therapeutic evaluation of these patients will be reported more fully in ORAU Medical Division Progress Report 1972 to be published in June 1973. Our evaluation of these patient's responses can be summarized as follows: Highly fractionated and low daily exposure rates:

1. Allow an opportunity to observe minimal untoward effects in time to alter the treatment plan.

2. Possibly enhance relative effect on malignant cells as compared with normal cell lines.

3. Permit relative effectivess on various lines of normal hematologic cells to be manifested.

4. Alter time course of effects so as to yield a more protracted beneficial effect, even from the single course of treatment. (The use of later repeated small doses was carried out successfully as a means of producing a prolonged, safe suppressive effect.)

TABLE 189.1972

CY-72 EXPERIENCE ADDITIONS

(see previous 189's or San Antonio National Academy Briefing Booklet, March 1972)

	METBI*			LETBI	
	Fraction 30 R/day	Random 30 R/day	Fraction 10 R/day	Continuous 30 R/day	Fraction 10 R/day
Previous					
(CY-67 -- CY-71)	17	0	2	44	7
CY-72	9	9	4	9	3
	—	—	—	—	—
	26	9	4	53	10

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*CY-1960 -- 1967: 82 prompt single exposures. Total 1967 - 1972: 182 case studies.

15. Progress in CY-72: (continued)

5. Seem to be producing further reduction in undesired side effects. (From the series of patients studied so far we can as yet give only tentative answers to the incidence of nausea and vomiting after low-dose-rate exposure because of the prominent variability in individual response to both single and fractionated exposures.)

Assessment of the hematologic effects of the new fractionated treatment regimes is still based on too few cases to allow valid generalizations. Our preliminary results suggest that protracted low-dose-rate exposures reduces the degree of cellular suppression. It appears, for example, that in chronic granulocytic leukemia treatment in METBI at 30 R/day to a total dose of 150 R produces somewhat less effect than 100 R given all at once, particularly upon granulocyte numbers. On the other hand, in one patient with CLL and in one with CGL, 10 R/day given in LETBI had a comparatively small effect on platelets, although a significant reduction in the leukocyte numbers was achieved.

Our results continue to suggest that protraction of the single course of therapy over a period of 5 to 15 days will not produce a prolonged, persistent suppression of the abnormal cell lines, but it appears, in our hands, that serial small follow-up doses of radiation will be effective in producing this effect (as demonstrated years ago by such workers as Osgood, Stone, and del Regato) and will allow better day-to-day control of the peripheral blood responses.

We are continuing to pursue our goal of obtaining a quantitative means of predicting the radiation response of normal man. Although human capabilities of marrow repair after radiation damage are relatively good, they seem to be greatly overestimated in *Radiobiological Factors in Manned Space Flight* (W. Langham, ed., National Academy of Sciences). Here (pp. 95-100) the ED_{50} are estimated for 50 percent depression in granulocytes, lymphocytes, and platelets to be 200, 150, and 125 rads. Our studies this year with continuous and fractionated exposures suggest that the ED_{50} for all types of blood cells is about 50 rad marrow dose for patients. Allowing a two-fold assumption of greater repairability of normal man would raise our estimate of 50 percent effective dose to only 100 rads. Moreover, since our observations are derived from responses to fractionated and protracted low-dose-rate exposure when repairability is expected to be higher than after a single, prompt exposure, this disagreement is actually worse than it appears. In continuing our attempts to obtain more human data at greater fractionated periods and lower doses, we are beginning to find daily dose sizes and radiation-free intervals between fractions where little or no effect on peripheral blood elements is obtained and therefore no clinical improvement is observed.

In CY 1972 we observed the courses of 32 patients; 12 were exposed in LETBI and 20 in METBI. Nine of the latter were exposed at intervals of 2 weeks to a month to 30 R in a day according to whether the attending physician felt that any previously obtained control of the disease was being lost. Under this regimen these patients received from 2 to 7 exposures to 30 R at 1.5 R/min. For the first time, some of these treatments were performed on an outpatient bais without interfering with the person's daily responsibilities. Two such

15. Progress in CY-72: (continued)

patients were exposed to only 10 R/day for the total doses of 50 and 100 R. The hematologic results of these small exposures were too short-lived to be considered therapeutic effects but were radiobiologically of great interest. The results here suggest that such exposures are within the repair capabilities of even the most radiation-sensitive diseased marrow.

In individual cases, for reasons we are still unable to discern, we continue to obtain unexpectedly brisk, extensive peripheral blood responses. For example, a previous untreated CGL exposed for the first time to 250 R at 30 R/day for 8.8 days responded with a >90% reduction in peripheral WBC count (240,000 down to about 14,000) within 2 weeks of the start of exposure. This change in granulocyte production was paralleled by an equally extensive platelet count diminution. Another example of this sudden unexpected response was obtained with a randomly timed 30 R exposure in a patient where previously two other 30 R exposures had been unable to abate a progressively rising peripheral granulocyte count. Following the third 30 R exposure (2 weeks after the previous one) both platelet count and granulcoyte count fell precipitously to less than normal levels where they have now remained for several months. Even with these exceptional cases, these fractionated and protracted exposures are proving to be as therapeutically useful and compare favorably with the best chemotherapy for these chronic diseases. In addition, this clinical radiotherapeutic approach using increasing low exposure rates is now providing us with numerous retrospective observations of effects in exposure situations that are increasingly more relevant to the occupational medical needs of deep space exploration where exposures are expected to be small, multiple, and randomly timed.

In the past year our efforts continued on developing and studying methods for assessing radiation-induced performance decrement objectively. In addition to repetitive physiological monitoring of additional irradiated patients to improve our detection system for radiation-induced gastrointestinal distress, we have studied changes in exercise capability of normal men using pulmonary responses to controlled exercise to obtain a data base for isolating the effects of radiation exposure on this system. Previously we found that increased respiratory efforts were required during controlled exercise periods one to two weeks after irradiation when exposures were protracted (30 R/day). Similar, but much more subtle changes, occurred during radiation therapy when the exposures were fractionated at 10 R/day. This year we found that regardless of the temporal format of the exposure protocol, irradiated patients developed an unexplained elevation in their pulmonary effort when at rest (amplified pulmonary impedance measured just prior to controlled exercise testing). This change may reflect biochemical events that are coupled with decrements in performance capability at a level that cannot be recognized by a person. The correlations of pulmonary impedance data with heart rate, creatine phosphokinase, and expired CO_2 before and after exercise in normal men and irradiated patients were studied during the past year.

15. Progress in CY-72: (continued)

Normal males (age 30-40 yr) were tested with controlled bicycling at workloads comparable to those of patients. In a typical study, each of five normal males exercised under controlled ergometry two or three times weekly for four consecutive weeks. The results are shown in Fig. 1 and demonstrate that normal man typically responds to moderate exercise by an increase in pulmonary impedance (as measured by its average variance). None of these volunteers had previous experience with bicycle ergometry. A decrease in the elevation of pulmonary impedance during controlled work developed progressively during the first several (~1-1/2 wk) exercise periods after which the exercise-induced response was relatively constant; probably due to adaptation to the exercise workloads. This effect is similar to "training" but differs from it in that 8 to 10 weeks would probably be required for training during which the work levels would be progressively increased. Virtually all individuals monitored in our laboratory show this decrease in pulmonary impedance response during their second and third exercise period. Normal volunteers, however, do not demonstrate an increase in pulmonary impedance in response to exercise in later exercise periods in contrast to irradiated subjects who all demonstrate such an increase some time during or after radiation exposure. Normal male volunteers also show less variable exercise recovery profiles (4-30 min post-exercise) as compared to irradiated patients where recovery time from exercise stress is not predictable.

Increase in serum creatine phosphokinase (SCPK) levels in normal volunteers exercising under our conditions (shown in Fig. 2) was found to be comparable to that reported in the recent literature for exercising men. Generally, SCPK levels rose 2-2.5 times the individual's preexercise test period levels. Although the SCPK levels remained above basal levels throughout the 4-wk test period, they appeared to be returning to normal during the fourth week again possibly due to adaption to a constant, rather than increasing, workload.

Serum creatine phosphokinase levels were determined in (a) irradiated patients who did not exercise; and (b) patients who were similarly exposed and tested by controlled exercise. In nonexercising patients exposed to 100 R (30 R/day, 1.5 R/hr) significant increases in serum CPK activity occurred during the exposure periods. The enzyme activity returned to normal within 2 weeks after exposure in all but one individual studied (Fig. 3). Similar changes in serum CPK activity were found in nonexercising patients exposed to 150 R in LETBI (Figs. 4 and 5). Only one of the patients exposed to 100 or 150 R failed to demonstrate the rise in serum CPK level. In nonexercising patients exposed using fractionated exposures (10 R/day LETBI) SCPK levels rose significantly in those receiving 150 R but not in one individual who received only 100 R. This increase in serum CPK activity was not evident until a few days (<1 wk) after irradiation and was of greater magnitude than in patients with similar but protracted exposures. These data seem to indicate that serum CPK level is highly dose-rate dependent and explain in part why the recent Oak Ridge radiation accident victim who received 260 rem (350 R/min) demonstrated a 12-fold increase in serum CPK level 3 days after irradiation at an extremely high dose rate (300 R/min).

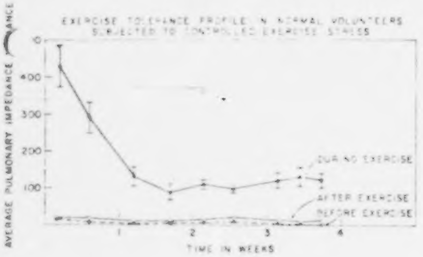

Fig. 1

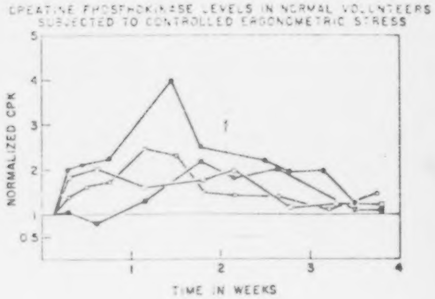

Fig. 2

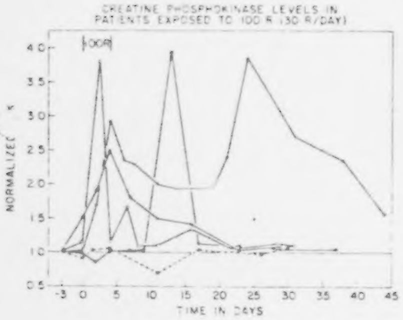

Fig. 3

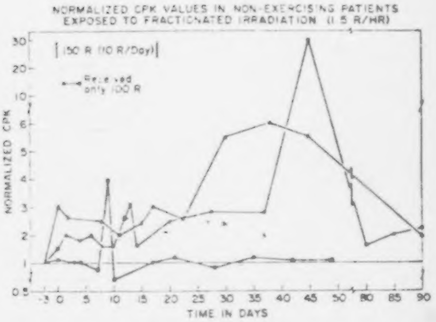

Fig. 4

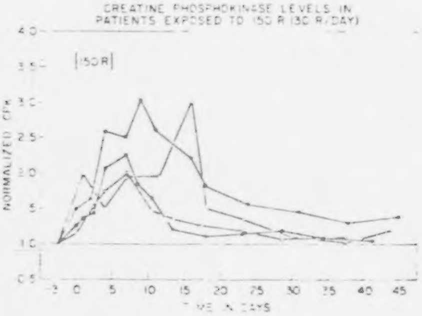

Fig. 5

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Project No.:

15. Progress in CY-72: (continued)

In one patient who demonstrated diminished exercise capacity during fractionated (10 R/day) irradiation therapy, a significant increase in serum CPK appeared to precede recovery from radiation-induced fatiguability (Fig. 6).

Our limited data on changes in serum creatine phosphokinase levels suggest that a relationship exists between exercise response and energy output levels (CPK dependent) but the timing between these events is not yet clear.

After several unsuccessful attempts due to failure of newly devised equipment, measurements of CO_2 concentration in the expired air of exercising subjects are now being made. It seemed likely to us that CO_2 levels might correlate with changes in the power spectra of pulmonary impedance during controlled exercise stress. Preliminary studies show that prior to controlled exercise our expired CO_2 measurements are within the normal levels reported for man (4.8%). Within less than 30 sec after initiation of controlled exercise the alveolar CO_2 rises ~25% to a value of 5.9%. Expired CO_2 levels remain elevated throughout the remainder of our exercise test period and when exercise is stopped, return within 2 min to preexercise levels. The increases and decreases in CO_2 levels correlate directly with the changes in the variance of the power spectra of pulmonary impedance during and immediately following exercise. The expired CO_2 level, however, returns to the preexercise level before changes in pulmonary impedance do. Increased alveolar CO_2 concentration also correlates well with elevated heart rate measured during exercise. Here again exhaled CO_2 concentration was found to return to the preexercise level ~12 times faster than heart rate. Table 2 illustrates these correlations between alveolar CO_2 concentration and heart rate in a normal volunteer subjected to controlled exercise testing. Figure 7 shows graphically this relationship between pulmonary impedance and CO_2 in one study.

Studies now in progress on two patients receiving 250 R (30 R/day, 1.5 R/hr) who are being subjected to controlled exercise stress indicate that the increase in alveolar CO_2 seems greater than expected after about 150 R are accumulated.

The first exercise tolerance profile was obtained this year on a patient undergoing treatment in the METBI facility (30 R/day, 1.5 R/min). This patient is the first woman who has participated in extensive exercise tests while receiving a total exposure of 250 R. The results, shown in Fig. 8, show that the variance of pulmonary impedance increased when 60 R were accumulated and was amplified for 7 days after irradiation. Exercise tolerance time was low (~2 min) prior to and through 18 days of controlled testing but had increased 3-fold when measured at 11 and 22 days after irradiation. Pulmonary impedance variance recorded before each exercise period (baseline data) show a slight but significant rise when 150 R were accumulated and remained elevated until 7 days after irradiation. The significance of a slightly amplified preexercise baseline is not clear at this time but could be due to anxiety, pain, or some unknown physiologic phenomenon that may increase basal pulmonary demand. Study of pulmonary impedance traces recorded on all patients exposed in LETBI (protracted exposures) shows an elevated baseline pulmonary impedance variance.

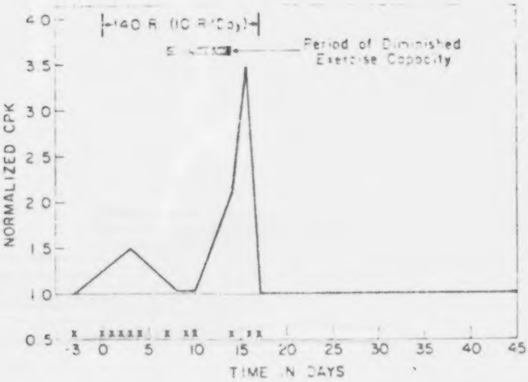

Fig. 6

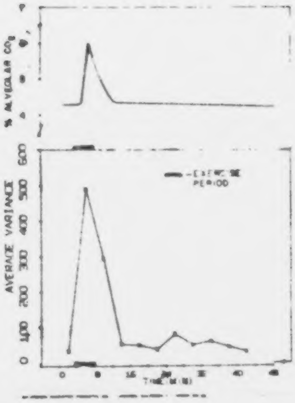

Fig. 7

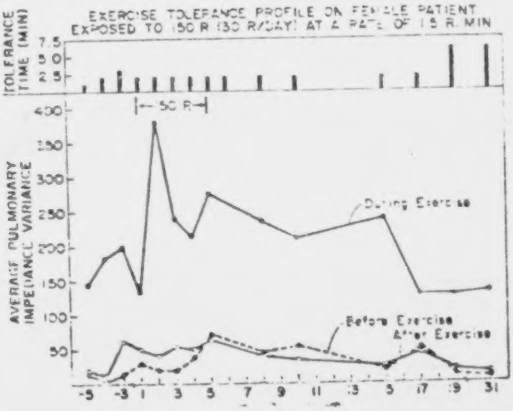

Fig. 8

TABLE 2

		Ratio of	
Monitoring Period	Pulmonary Impedance Variance	CO_2/ basal CO_2	Heart rate/ basal heart rate
Pre-exercise (1)	41	1.00	1.00
During exercise	497	1.45	1.70
End exercise + 4 min	301	1.25	1.20
" " + 8 min	61	1.01	1.13
" " + 12 min	58	1.00	1.12
" " + 16 min	46	1.00	1.07
" " + 20 min	64	1.00	1.08
" " + 24 min	51	1.00	1.08
" " + 28 min	65	1.00	1.05

(1) Data measured at 4 min prior to bicycle ergometry (50 watt workload).

15. Progress in CY-72: (continued)

This elevation is most evident in patients exposed to 250 R (30 R/day). While patients exposed to 150 R and 100 R show slightly elevated baselines, it does not seem dose-rate dependent. Figure 9 shows that the elevation of baseline pulmonary impedance of resting, nonexercise stressed patients is highly variable in comparison with that or normal unirradiated men. These observations of changes in respiration, serum levels of a muscle enzyme, cardiac rate, and alveolar CO_2 during stress after irradiation suggest that we may have an objective means of measuring diminished exercise capacity in persons exposed to total-body ionizing radiation. The number of persons studied is still insufficient for creating a quantitative dose-response model. Results to date indicate that (1) protracted exposure (LETBI) of 100 or 150 R result in diminished exercise capability (DEC) within 1-2 weeks after exposure; (2) fractionated exposures (10 R/day, METBI) result in DEC during the exposure period starting about when ~40 R have been accumulated. This effect seems to subside after 100 R; (3) fractionated exposures of 30 R/day (METBI) produce DEC starting early in the exposure period (~60 R accumulated) and lasting for its duration (e.g., 5 days for 150 R). The relative severity of DEC (based on pulmonary changes appears to be: >>> 30 R/day (1.5 R/min) >> 30 R/day (1.5 R/hr) > 10 R/day (1.5 R/hr). Changes in exercise capacity in a radiation accident victim were more comparable to patients receiving 30 R/day (1.5 R/min) than any other doseage group of patients.

All individuals (patients and normal volunteers) demonstrated significant increases in serum creatine phosphokinase levels when subjected to controlled exercise stress and/or irradiation. These studies are incomplete at this time so that direct correlations cannot be made of the level of circulating CPK with periods of diminished exercise capability. The increase in circulating CPK level may be a feedback systemic response to stress that works to prevent or delay fatiguability but further studies will be required before any such role can be substantiated for it.

Changes in heart rate have not been as reliable an indicator of fatigue as changes in pulmonary impedance have been in patients undergoing irradiation and controlled exercise testing. Increases in heart rate in both normal volunteers and patients appear to relate only to the level of exercise workload and not to periods of fatigue. Our most sensitive indicator of fatiguability remains the average variance of pulmonary impedance. Heart rate data correlate with this measurement only during exercise. With the addition of our capability to measure alveolar CO_2 externally, we anticipate that we will see different patterns of correlation between CO_2, heart rate, and pulmonary impedance in the irradiated, exercise-stressed patient during periods of increased fatiguability.

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16. Program Plans for CY-73:

Analyses of the results of our new clinical regimens of increasingly smaller daily radiation doses randomly spaced in time suggest that we focus our efforts this year on defining more precisely, than has as yet been possible, the lower threshold of human radiosensitivity and individual variation in responsiveness.

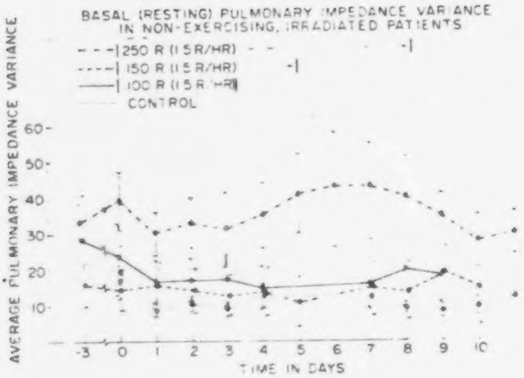
BASAL (RESTING) PULMONARY IMPEDANCE VARIANCE
IN NON-EXERCISING, IRRADIATED PATIENTS
250 R (1.5 R/HR)
150 R (1.5 R/HR)
100 R (1.5 R/HR)
CONTROL
AVERAGE PULMONARY IMPEDANCE VARIANCE
60
50
40
30
20
10
-3
0
1
2
3
4
5
6
7
8
9
10
TIME IN DAYS

Fig. 9

16. Program Plans for CY-73: (continued)

We will continue to use peripheral blood cell levels and the perturbations in their numbers as the major indices of response and marrow capabilities for cellular repair and systemic reconstitution.

We propose continued study of the cross correlations of the enzymatic, respiratory, and cardiac changes that we find characterizes periods of radiation-induced fatigue. New systems of retrospective analysis have been developed but not yet employed to make three-dimensional correlations between pulmonary impedance, CO_2 production, and muscle enzyme levels. The temporal relationship of changes in cardiac and pulmonary function during exercise stress and exercise recovery periods will be studied to determine the effect of irradiation on subjective work levels. While the change in the level of pulmonary function seems to us to be the determining factor during recovery of cardiac function after exercise stress, no one has yet studied whether the system of defining a person's level of work by cardiac rate (for example, 120 beats/min = light work; 160 beats/min = heavy work) can be improved or sensitized by combining it with measurements of pulmonary effort. We will thereby contrast the effectiveness of these low dose rates and low doses on:

1. The lower threshold of human radiosensitivity for:
    a. Hematopoietic system
    b. Neurophysiologic system
        (1) Gastrointestinal
        (2) Muscular work and fatiguing systems
2. Human repair capabilities of:
    a. Cellular systems
    b. Physiologic (biochemical) systems
        (1) CPK - muscle enzyme response
        (2) Glycoprotein and abnormal and protective substances (e.g., serum antitrypsin)

As proposed previously for CY-73 (see 189.71, page 21), we shall decrease the dose rate in LETBI from 1.5 R/hr to 0.8 R/hr or less. This decrease will result in a maximum daily protracted dose of about 15 to 16 R/day. This dose and rate should approximate the radiation marrow damage level that average man can repair and thereby make a steady state adaption to over a period of several weeks or months. Therapeutically this type of exposure could conceivably promote normal cellular repair processes at the expense of radiosensitive malignant marrow cells. If so, this kind of radiation exposure might be employed to hold steady the level of marrow activity produced by irradiation in METBI

16. Program Plans for CY-73: (continued)

at a higher dose delivered at a faster rate. In the context of basic human data requirements for evaluation of radiation incidents in space exploration, this information would help in setting guidelines for using occupational constraints during emergencies (as during uncontrollable solar events or nuclear accidents). Medical decision-making could be based on the previous records of response of an individual astronaut to his exposures instead of on fixed cut offs at maximum permissible levels constraining his career. We anticipate that these prolonged exposures (two to three weeks) will produce little or no undesirable gastrointestinal effects but will be complicated by increased fatiguability due to both radiation exposure and spatial confinement. This problem will be met by the physiologic ergometry program that will provide controlled performance exercises beneficial to the patient while providing us data on rates of performance decrement under hostile environmental conditions. Sera, blood, body fluids, and excretory samples will be available for measuring metabolites of interest under these confined conditions. Clinical and laboratory evaluations of progress will be correlated as closely as possible with individualized radiation depth dose measurements obtained from shadow shielding studies using the patient's own body mass.

17. Program Plans for CY-74:

Major emphasis will be placed on consolidation of our previous analyses of our data and extending these observations and their suggested applications as clinical opportunity affords. Specifically, we will complete an atlas of typical human hematologic responses of patients to various doses and rates and of the projected course of events these curves suggest for normal man. A fascicle will be prepared reviewing our clinical experiences and summarizing our retrospective analyses in hematology and remote physiologic monitoring. In addition, we will continue our attempts to measure fatigue in cognitive effort by objective means. We are presently investigating the possibility of adapting present methods of computer-assisted instruction to this problem. It appears feasible to have a remote computer input console and oscillograph display within the LETBI facility so that during low-dose-rate exposures cognitive processes could be tested under preprogrammed conditions. Conceivably, simple tasks requiring little or no physical effort (for example, driving on a simulated road, multiple choice tests, or problem solutions) could be used. By comparing results from day-to-day using objective computerized analyses, changes in learning rates, fine muscular performance, etc. could be detected and related to radiation dose accumulation in relation to disease status and gross fatiguability. This study would attempt to measure the well known increase in error making that occurs with biochemical changes in brain, blood fluids, and muscle during fatigue and determine whether there is a dose-response relation with irradiation.

2. Project Title: Radiosensitivity in Man: Project No:
A Study of Therapeutic and Accidental
Whole-Body Irradiation

18. Significant Capital Equipment:

The total available budget does not permit planning again this year (CY-73) for major expenditures for capital equipment. It is anticipated that the physiological monitoring devices and computer interfacing electronics and memory systems that we are now using will, for the most part, be adequate for continuing these studies at their present level. In CY-74, however, if our feasibility study in CY-73 of computer-assisted memory testing and performance proves favorable, oscillograph display and a computer interfacing unit (for existing IBM 1800 system) would be needed (approximate cost: $8,000 - $10,000).